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CHRONIC AORTO-ILIAC OBSTRUCTION*

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THIS STUDY of 30 patients with chronic aorto-iliac obstruction was primarily undertaken to determine the role of aortic graft surgery in the treatment of this condition. Observations on the clinical features, pathological findings and natural course will be reviewed as well as the preliminary results of surgical therapy.

SELECTION OF PATIENTS

Since the clinical picture and treatment of occlusion of the terminal aorta (Leriche syndrome) and of bilateral high iliac obstruction are similar, the two will be discussed together. To avoid errors in clinical diagnosis, only patients in whom the condition was confirmed by aortography have been included.

DATA ON PATIENTS

In this group, there were 27 men and three women (a sex ratio of nine to one). More than half the patients suffered the initial symptoms before the age of 50 (Table I) and about 80% dated the onset before 60 years of age. The coexistent medical conditions recognized in this group of patients are listed. The high incidence of coronary disease observed was not unexpected because of the common etiology.

SYMPTOMS

The prominent symptoms are listed in Table II. Intermittent claudication was the chief symptom and occurred in all patients. In three patients in whom the onset of claudication was abrupt, there was no apparent source for an embolus. The features which tend to distinguish the claudication of this condition from that due to obstruction of the arteries lower in the leg are its symmetrical distribution, the involvement of the thighs and buttocks, and the fact that patients often complain of fatigue or heaviness of the legs as the most distressing symptoms.

TABLE I.—DATA ON THIRTY PATIENTS WITH CHRONIC AORTO-ILIAC OBSTRUCTION

		Patients
1. *Sex* 27 men, 3 women		
2. *Age at onset*		
Range	36 - 66	
Average	50	
No. under 50		16
3. *Coexistent disorders*		
Coronary disease		11
Hypertension (160/90)		6
Peptic ulcer		5
Diabetes		2
Tuberculosis		1

TABLE II.—PROMINENT SYMPTOMS OF PATIENTS WITH CHRONIC AORTO-ILIAC OBSTRUCTION

		Patients
Intermittent claudication		30
Onset:	gradual	27
	unilateral	20
	below knee only	7
Later:	both calves and thighs	24
	hips and buttocks	19
Rest pain		10
Impotence		16 (of 22)
Backache		9
Gangrenous changes		3

Pain at rest occurred in one-third of the group, usually as a late phenomenon associated with severe intermittent claudication. Although sexual desire was not impaired, difficulty in maintaining a satisfactory erection was complained of by 16 out of the 22 men in whom reliable data on this aspect were obtainable. Leriche attributed this to inadequate blood flow through the pudendal branches of the internal iliac arteries which supply the penis.[1]

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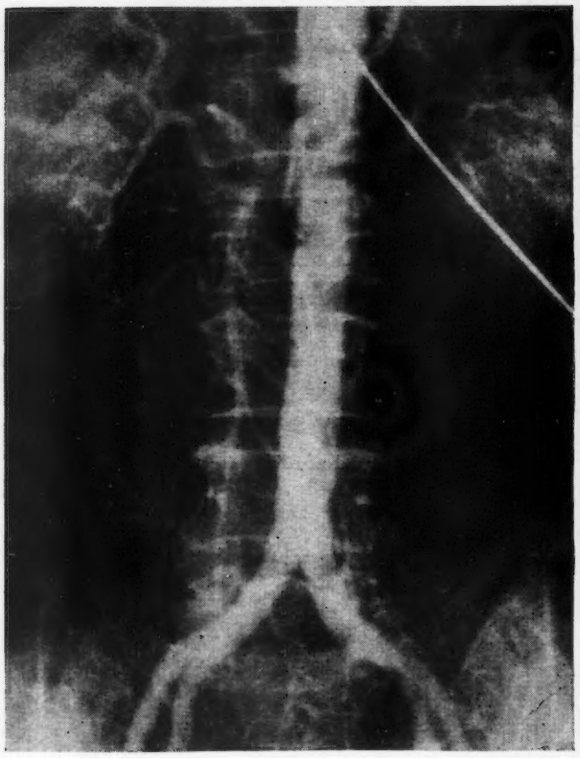

Fig. 1.

Fig. 2.

Fig. 1 is a normal translumbar aortogram. Fig. 2 demonstrates complete obstruction of the abdominal aorta below the level of the renal arteries.

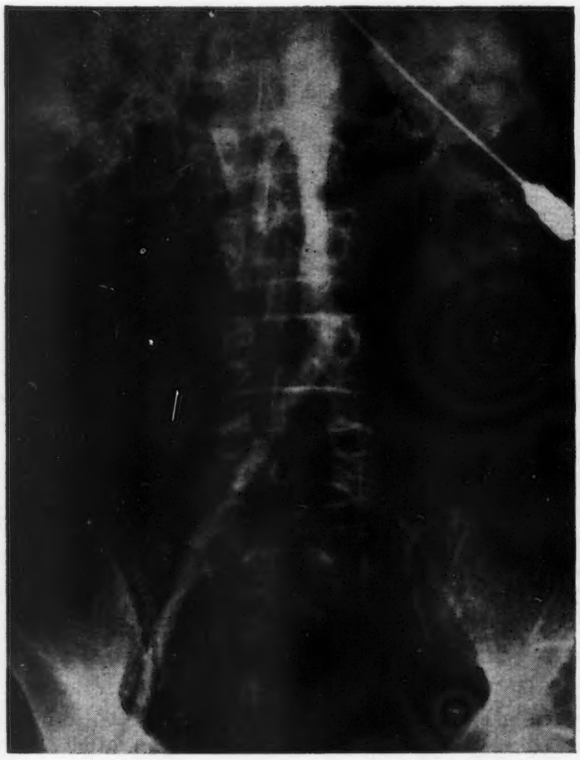

Fig. 3.

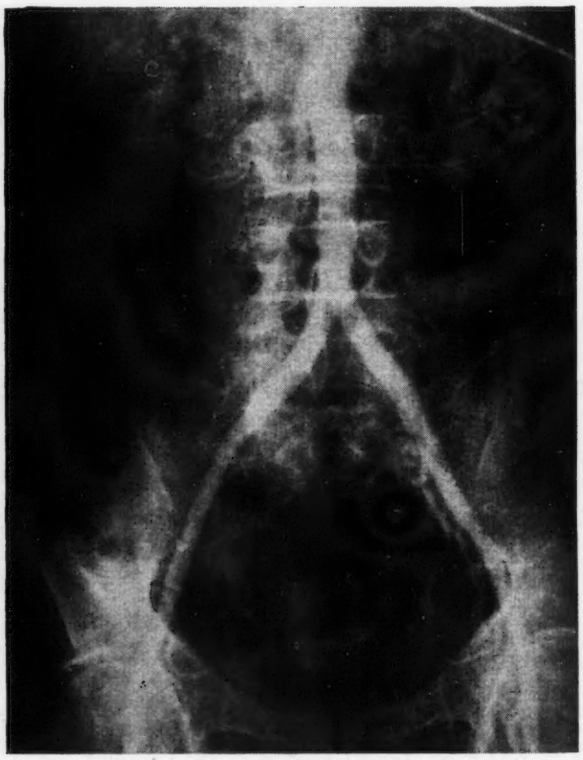

Fig. 4.

Fig. 3 reveals narrowing of the aorta below the renal arteries with narrowing of the right common iliac artery and a segmental block of the left common iliac. Fig. 4 is an aortogram of the same patient as in Fig. 3 three months after aortic graft surgery.

Nine patients complained of a lumbar backache which was aggravated by bending and prolonged sitting, and superficially resembled the extruded lumbar intervertebral disc syndrome. This has been recognized before in patients with occlusion of the aorta and has been attributed to periaortitis, ischæmia of lumbar muscles, etc.[2]

Of the three patients with gangrenous changes, one had undergone amputation of a toe, one presented with an ischæmic ulcer of the heel and the third came to mid-thigh amputation. A fourth patient had persistent bluish discoloration of two toes on one foot that were considered to be in a pre-gangrenous state. Coldness and night cramps were frequent symptoms.

PHYSICAL EXAMINATION

Absence of pulsation was the most constant physical abnormality (Table III). None of the patients had a normal femoral pulse on both sides. In two patients with complete occlusion of the terminal aorta, the posterior tibial pulse was easily felt, indicating a highly developed collateral circulation. Although prolongation of venous filling time is common in arterial insufficiency, a normal value is not unusual with high arterial occlusion. Abnormal blanching on elevation of the leg and/or unusual rubor on dependency was observed in 24 of 27 patients. A systolic bruit was audible over one or both femoral arteries, in the lower abdomen or over the sacrum in 14 of 19 patients who were examined carefully for this sign. Occasionally, a bruit could be heard in the groin when the femoral pulse was not palpable. Such a bruit is presumably caused by blood flowing in superficial collateral arteries. Coldness of the feet on palpation was found in nearly every patient. Nutritional skin changes such as loss of subcutaneous fat, loss of hair and thickening of toenails were observed in varying combinations in about two-thirds but were seldom striking in degree. Unequivocal loss of muscle bulk in the thighs or calves was noted in about 20%. Symmetrical wasting of the legs (so-called "global atrophy")[3] was recognized with certainty in only one instance.

ANGIOGRAPHY

The findings on translumbar aortography are summarized in Table IV. In 22 patients, these were confirmed at operation. Figs. 1 to 4 are representative of the abnormal aortograms with a normal aortogram for comparison. One patient developed abdominal cramps, vomiting, and swelling of the liver and salivary glands the day after her aortogram. These symptoms subsided over the next five days. This was the only untoward reaction possibly related to aortography in this group.

TABLE III. — EXAMINATION OF 30 PATIENTS WITH CHRONIC AORTO-ILIAC OBSTRUCTION

Pulsations	*Patients*
Normal femorals bilaterally	0
All leg pulses absent	17
Venous filling time:	
More than 20 sec.	12 of 22
Postural colour changes	24 of 27
Systolic bruit	14 of 19
Coldness of feet	21 of 24
Trophic skin changes	18 of 29
Muscle wasting	6 of 26

PATHOLOGY

Pathological examination of the specimens was possible in 12 instances. In one, the terminal aorta appeared hypoplastic as if due to a congenital coarctation and in two, thrombotic occlusion was superimposed on arteriosclerotic aneurysms. In the remainder, advanced atherosclerosis was the condition underlying the thrombosis.

In one of the six patients with hypertension, thrombosis had ascended and obstructed the left renal artery. Removal of this kidney restored the blood pressure to normal and it has remained normal for two years since the nephrectomy.[6]

Extension of the thrombus in the aorta with involvement of the renal arteries has been previously described by Spaulding.[4]

NATURAL COURSE

Since this review does not include patients whose symptoms were insufficient to justify aortography, and since the majority of our 30 patients have received special treatment, these

TABLE IV.—NATURE OF BLOCK IN PATIENTS WITH CHRONIC AORTO-ILIAC OBSTRUCTION

	Patients
Complete occlusion terminal aorta or both common iliacs	16
Narrowing of aorta and complete block one common iliac	8
Narrowing of aorta and iliacs but no complete block	6
Total	30

patients do not afford a true picture of the natural course.

Fifteen patients were severely disabled as evidenced by pain at rest, gangrenous changes or claudication that prevented them from working or enjoying life. Thirteen patients were moderately disabled by claudication, although they were able to work with difficulty. The fact that the average duration of symptoms was five years indicates the chronicity of this disease (Table V).

TABLE V.—"NATURAL" COURSE OF PATIENTS WITH CHRONIC AORTO-ILIAC OBSTRUCTION

Duration of symptoms	*Patients*
Range ..... 7 wk. - 18 yr.	
Average ..... 5 yr.	
Spontaneous improvement	2
Symptoms increased	28
(a) One leg to both legs	14
(b) Extension of involvement, same limb(s)	10
(c) Same site but more severe	6
(d) Developed rest pain	8
(e) Developed gangrenous changes	3

Two patients had spontaneous remission of symptoms that initially had been severe enough to justify aortography. In the remainder, the condition was apparently slowly progressive. This deterioration was usually insidious and although one patient became worse within weeks of the onset, two years was the average interval before aggravation of symptoms was noticed. The fact that 70% of the group who began with unilateral complaints eventually developed bilateral involvement supports the concept that occlusion of the terminal aorta often begins as obstruction of one common iliac that extends proximally.[3]

Of the 11 patients with manifestations of coexistent coronary atherosclerosis, four suffered myocardial infarctions or the onset of angina pectoris during the period of observation. This is an important consideration in the prognosis of this condition.

TREATMENT

In seven patients given a thorough clinical trial with a variety of drugs such as vitamin E or vasodilators, there was no conclusive evidence that the symptoms were significantly affected. One death occurred in this group; a 68-year-old man with coronary disease died after amputation for intractable rest pain. Three patients were subjected to lumbar sympathectomy, two of whom were unimproved. The third showed no benefit for two years after operation but then, over a period of six months, developed hypertension and became free of symptoms. It is doubtful if this improvement can be credited to the sympathectomy after such a long latent period.

Twenty patients were treated by aortic graft surgery. The grafts used were Y grafts consisting of the terminal aorta and ilio-femoral trunks obtained from autopsy material. In a few patients, lumbar sympathectomy was performed at the same time, in some endarterectomy of the host vessel was necessary before anastomosis could be accomplished, and in 12 the occluded segments were excised. Five patients had a second operation—in three cases this was for thrombosis of one limb of the graft, and in the remaining two the second operation was to control hæmorrhage. Of 21 patients considered for graft surgery, only one was found unsuitable because of advanced disease of the ilio-femoral vessels.

There were three postoperative deaths: one (three months later) due to hæmorrhage from disintegration of the graft, one from acute renal failure (18 months after first operation, 10 days after the second), and one to septicæmia with rupture of a mycotic aneurysm of the graft (18 days). These are listed in Table VI.

TABLE VI.—COMPLICATIONS FOLLOWING AORTIC GRAFT SURGERY FOR CHRONIC AORTO-ILIAC OBSTRUCTION

	Patients
Myocardial infarction	1
Uræmia with recovery	1
Deaths	3
(a) Uræmia	1
(b) Hæmorrhage	1
(c) Septicæmia and hæmorrhage	1

RESULTS OF TREATMENT

The time elapsed since aortic graft surgery in these patients varies from four weeks to two years, with an average of 10 months. Immediately after operation, all showed a return of one or more of the pulsations that had been previously absent. This pulsation has disappeared again in only three patients. The present status of these 20 patients is summarized in Table VII. Of the two patients who are unimproved at the present time, one was free of intermittent claudication for one year, at which time his symptoms returned and he developed angina pectoris that limits his walking as much as did his claudication. For this reason, he has not been subjected to another graft operation.

TABLE VII.—PRESENT STATUS OF TWENTY PATIENTS WITH CHRONIC AORTO-ILIAC OBSTRUCTION TREATED BY AORTIC GRAFT SURGERY

Present status	*Patients*
Improved	15
Unimproved	2
(1 free of claudication for 1 year)	
Dead	3
(1 improved for 18 months)	
(1 relieved for 1 month)	
Total	20

The effect of aortic graft surgery on 19 patients followed up from four months to two years is presented in Table VIII. Eleven patients are completely free of claudication and three others have substantially increased walking capacity. Three of four patients treated surgically, who had rest pain, had relief of this symptom. Two pregangrenous lesions responded well to treatment: (1) an ischæmic ulcer on the heel and (2) permanently discoloured toes. Three of nine men with sexual impotence were relieved of this symptom after operation.

TABLE VIII.—EFFECT OF AORTIC GRAFT SURGERY ON SYMPTOMS OF PATIENTS WITH CHRONIC AORTO-ILIAC OBSTRUCTION

Symptom	*Patients*
Intermittent claudication	
Complete relief	12
(1 recurred at 1 year)	
Partial relief	3
Unimproved	1
Total	16
Rest pain (4 patients)	
Relieved	3
Pregangrenous lesions (2 patients)	
Recovery	2
Impotence (9 patients)	
Relieved	3

SUMMARY AND CONCLUSIONS

Thirty cases of obstruction of the terminal aorta or iliac arteries are reviewed. The clinical features and findings on aortography are presented. Eleven patients had demonstrable evidence of coexistent arteriosclerotic heart disease. Although two patients improved spontaneously, this condition is characterized by insidiously increasing disability from intermittent claudication and rest pain. Ulcerative lesions were infrequent. A number of these patients were given a variety of drugs with no significant effect on the symptoms.

Twenty of 21 patients in this series were found to have lesions anatomically suitable for aortic graft surgery. There were three deaths in 23 aorto-iliac graft operations (mortality 13%) and one death in 10 patients not subjected to this treatment. Postoperative complications such as hæmorrhage, myocardial infarction and uræmia have been encountered.

Striking improvement from the initial graft operation was observed in 14 of 20 patients; after a second graft, an additional two patients were relieved of intermittent claudication. Late failure (12 and 18 months postoperatively, respectively) has occurred in two of these 16 patients. Rest pain was relieved in three of four patients. In two patients, pregangrenous lesions healed postoperatively and three of nine impotent men had a return of sexual power.

A correct diagnosis of this condition can usually be made on the clinical features. Confirmation may be obtained by translumbar aortography, but this is not indicated unless surgical measures are to be undertaken. As a result of this experience, aortic graft surgery is suggested for patients whose segmental aortic obstruction is causing (1) actual or incipient gangrene, (2) rest pain and (3) intermittent claudication that materially interferes with the capacity for work or with the patient's morale. This group represents approximately half the patients with this condition who have been studied by our group. In patients who fulfil one or more of these criteria, aortic graft surgery is considered the most effective therapy available.

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RÉSUMÉ

Cet article est une revue de 35 cas d'obstruction de l'aorte terminale ou des artères iliaques. Les faits cliniques ainsi que les données de l'aortographie sont présentés. Onze de ces malades montraient aussi des signes de maladie de cœur artério-sclérotique. Même si deux malades accusèrent une amélioration spontanée, cette affection n'en est pas moins caractérisée par le progrès insidieux d'une incapacité résultant de la claudication intermittente et de la douleur au repos. Les lésions ulcéreuses sont rares. Un certain nombre de ces malades reçurent différents médicaments sans modification appréciable de leurs symptômes.

Les lésions anatomiques de 20 malades, de cette série de 21, furent considérés comme pouvant se prêter à la greffe aortique. Trois des 23 malades opérés ne survécurent pas à l'intervention pour greffe aorto-iliaque, donnant ainsi une mortalité opératoire de 13%. Par contre, un des 10 malades non opérés mourut aussi. L'hémorragie, l'infarctus du myocarde et l'urémie se comptèrent au nombre des complications post-opératoires.

Une amélioration frappante fut observée chez 14 des 20 patients dès la première intervention de greffage; deux autres malades furent débarrassés de leur claudication intermittente après une seconde opération. Le traitement s'est soldé par un échec à longue échéance chez deux de ces 16 malades, 12 et 18 mois respectivement après l'opération. Trois des quatre malades affligés de douleur au repos, furent soulagés. Les lésions prégangreneuses de deux malades disparurent après l'opération et la puissance sexuelle revint à trois des neuf malades qui l'avaient perdue.

On peut habituellement arriver à un diagnostic d'après les faits cliniques. La confirmation que peut apporter l'aortographie translombaire ne doit être recherchée que si l'on a décidé de procéder à l'opération. Les données de l'expérience dictent que la greffe aortique peut s'appliquer aux malades dont l'obstruction aortique segmentaire a déjà causé (1) de la gangrène ou est en instance de le faire (2) de la douleur au repos (3) de la claudication intermittente ayant un sérieux retentissement sur la capacité de travail du malade ou sur son moral. Ces caractères s'appliquent à environ la moitié des malades examinés par les auteurs de cet article. Les malades présentant une ou plusieurs de ces infirmités sont considérés comme des candidats pour qui la greffe aortique est la meilleure forme de traitement possible.

SLIDING HIATUS HERNIA—A REVIEW OF CASES*

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THE WORK of Allison of Leeds,[1] Johnstone,[2] and Barrett[3] has focused attention on the problem of hiatus hernia of the sliding variety, illuminated the pathology of the cardia and given a rational, although perhaps still incomplete, explanation of the mechanism of continence at the cardia. The most important factor in the maintenance of continence at the cardia appears to be the existence of the normal acute angle made by the œsophagus with the stomach, which is lost in sliding hiatus hernia.[4]

Sliding hiatus hernia is not an uncommon condition, and if looked for will provide a rational explanation for symptoms in many patients hitherto considered as suffering from some vague gastric disturbance usually classified as psychoneurosis, hyperchlorhydria, duodenal ulcer without radiological evidence, gastritis, or functional dyspepsia. Brick and Amory[5] surveyed 3448 patients with gastro-intestinal symptoms by x-ray investigation of the upper gastro-intestinal tract. Duodenal ulcer was found in 705, and hiatus hernia was found in 308, of whom 82% were over 50 years old. This gives an incidence of 9% in people with symptoms. Three hundred people without symptoms were investigated and four hiatus hernias were found, an incidence of 1.3%. This investigation alone, incomplete as it was, indicates that hiatus hernia must be carefully considered before it is dismissed as of no account.

The publication of Allison's results[1] and the fortunate coincidence of recognition of the syndrome shortly afterwards aroused our interest in these cases, and in the past five years 108 patients have been seen with this lesion. Five paraœsophageal hernias were also seen during this time, but are not included in this series. The majority of this series would not have been recognized if it had not been for the enthusiastic co-operation of the internists and radiologists.

The series is not statistically significant, as it is distinctly a loaded one, since the majority of the patients were seen at Deer Lodge Hospital, almost exclusively an institution for male patients. Nevertheless, it has been divided throughout into private and Department of Veterans Affairs patients, in order that some difference aside from sex may be observed, and merely constitutes a record of personal experience in dealing with these patients.

The operation described by Allison fulfils the principles of hernia repair applicable to any hernia—removal of the sac and repair of the defect. In addition, we believe that the sutures placed between the diaphragm and cut edge of the phreno-œsophageal ligament aid in maintaining the normal angle of the œsophagus with the stomach by ensuring that the normally abdominal portion of the œsophagus remains so. We do not believe that suture of the fundus of the stomach to the diaphragm is rational or necessary. We have employed the operation as described by Allison, with only one minor change in technique, which does not affect the principles of the operation.

TABLE I.
No. of Patients

DVA patients	88
Private patients	20
Total	108

TABLE II.
Operations

DVA patients	12
Private patients	12
Total	24

In the past four years 108 cases of sliding hiatus hernia were seen, 88 at Deer Lodge and 20 privately. With the exception of two patients who were referred in the private

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series, the private cases were those which might be seen in a group practice. The majority of the patients seen at Deer Lodge were being investigated for gastro-intestinal complaints, many of them of long standing, and for which many were pensioned under various diagnoses. The remainder were discovered on routine investigation, where a barium series was done. All the private patients complained of definite gastro-intestinal symptoms, and in nearly all the history indicated the possibility of a sliding hiatus hernia.

TABLE III.

Sex distribution		*DVA*	*Private*
Male	94	87	7
Female	14	1	13

Of the total series 94 were male and 14 female. Eighty-seven male patients were seen at Deer Lodge, and seven were seen privately. The figures seen in private practice probably come close to the ratio which one might expect in the population with symptoms referable to the gastro-intestinal tract.

The age distribution in the series is interesting, the range being from 22 to 82 years of age. In the DVA series, the majority of the patients

TABLE IV.

Age distribution	*DVA*	*Private*
Range	22 - 82	24-72
20 - 29	6	1
30 - 39	3	6
40 - 49	9	3
50 - 59	9	4
60 - 69	33	3
70 - 79	23	3
80 and over	5	0
Total	88	20

TABLE V.

Operative series: age distribution	*DVA*	*Private*
20 - 29	3	1
30 - 39	1	4
40 - 49	2	2
50 - 59	3	4
60 - 69	2	0
70 - 79	1	1
80 and over	0	0
Total	12	12

were in the 60 to 80 years age group (61 out of 88). The number of private patients is insufficient to draw any conclusions about age distribution. It is important not to regard hiatus hernia as a lesion occurring solely in the middle-aged or elderly; seven of our patients were under 30, and of these seven, four were operated on after failure of medical conservative treatment. This is an operative incidence much greater than that in the group as a whole (24 out of 108).

As might be expected from the age distribution of the majority of patients, the matter of associated illnesses is very important, both in assessing the relative importance of the hernia and in determining fitness for operation. Many of these patients had several associated lesions, and consequently the total number of lesions exceeds the total number of patients. Only the most important illnesses have been listed and they have been grouped as far as possible.

TABLE VI.—Associated Illnesses

Non-operative series		*Operative series*	
Mental	9	Tension state	2
Obesity	4	Obesity	2
Cardiovascular	29	Cardiovascular	2
Pulmonary disease	10	Pulmonary sepsis (mild)	3
Hæmorrhage (GI)	14	Arrested pulmonary tuberculosis	1
Carcinoma—stomach	1	Carcinoma sigmoid (cure?)	1
pancreas	2	Duodenal deformity	2
Peptic ulcer	14	Duodenal ulcer	3
Gall-bladder disease	3	Gall-bladder disease	3
Pancreatitis	1	Pancreatitis	1
Prostatic disease	3	Cystic disease, liver, kidney, pancreas	1
Severe arthritis	3	Alcoholism	1
Ectopic gastric mucosa with hæmorrhage	1	Congenital dislocation hips	1
Malignant melanoma	1	Œsophageal stricture	2
Other hernia	2	Ectopic gastric mucosa with ulceration	1
Œsophageal stricture	1		

The high incidence of cardiovascular, mental or pulmonary lesions might be expected in such a group. It is also shown that symptoms from a hiatus hernia with œsophagitis may be so distressing as to justify operation in the presence of lesions which in themselves demand treatment but are not considered to be the source of the major complaints. Perhaps the most difficult problem here has been the association of duodenal ulcer or duodenal cap deformity, gall-bladder disease, and in three cases (one of which was operated upon) proved pancreatitis. One patient of the series operated on will require surgical treatment for duodenal ulcer owing to his inability to maintain a proper medical regimen. His symptoms of reflux œsophagitis have been cured, and he now has the typical pain of duodenal ulcer. His result has been counted as fair.

All the patients in the operative series gave a history of classical symptoms of reflux and œsophagitis. Of the 84 not operated upon, five had atypical symptoms not considered due to their hernia, 15 were asymptomatic and the hernia was discovered routinely, 36 were controlled medically, eight were not treated, and 20 were thought to be not fit for operation because of severe associated disease.

There were 11 deaths in the non-operative series, the major causes of death being coronary occlusion and gastro-intestinal hæmorrhage. It is interesting to note that two of the three deaths from gastro-intestinal hæmorrhage were due to bleeding from the œsophagus. There were no operative deaths in the series.

Diagnosis

Barium series demonstrated the presence of a hiatus hernia in all the patients not operated upon, and in 18 of the operative series. In six of the operative cases, the x-ray examination did not show a hernia, but on œsophagoscopy the excursion of the gastric mucosa was definite and associated œsophagitis ranged from mild to ulcerative with leukoplakia. This is an important point in diagnosis; if the symptoms indicate a hiatus hernia with reflux, the findings on radiography should not be accepted as final. Three of our best results and one fair result fall in this group.

Operations

There was a total of 24 operations, 12 of which were done at Deer Lodge Hospital (DVA) and 12 in private practice at several hospitals. One case was repaired from below by another surgeon and it is not included in the series.

Patients for operation were selected on the basis of a demonstrable hiatus hernia of the sliding variety, classical symptoms not relieved by medical treatment, and the presence of œsophagitis. Only one patient operated on had a stricture and it was a short, easily dilated one. The presence of associated disease did not rule out operation if it was felt that the symptoms were disabling and medical treatment had failed. Many of the patients had had various medical regimens for years with little or no improvement, and welcomed something being done for them. Patients were refused operation in the presence of severe cardiovascular disease, severe cerebral lesions, and associated neoplastic disease—conditions which would normally contraindicate elective operation for mechanical defects.

Postoperative Complications

TABLE VII.—Postoperative Complications

DVA		*Private*	
Nil	5	Nil	8
Atelectasis	3	Atelectasis	2
Pulmonary sepsis	2	Intestinal obstruction	1
Chest pain	1	Acute pancreatitis	1
Wound infection	1	Wound infection	1

There were no postoperative complications in 13 out of the 24 operated on. Five patients had atelectasis of varying degree, one of which was severe and required bronchoscopy. The other four rapidly responded to the usual conservative measures. Two had postoperative pneumonitis, one of severe degree. After 28 months, this patient still complains of shortness of breath and his x-ray films show some pulmonary fibrosis and pleural thickening. Psychologically he is not the ideal patient, and the medical department does not view his pulmonary impairment as serious. One patient is listed as having intestinal obstruction postoperatively, and this requires some explanation. She was an elderly woman with cholelithiasis, a duodenal ulcer and a total gastric acidity of 179 units. In addition to the Allison repair, a vagotomy and gastro-enterostomy were done, and the patient developed an obstruction in the efferent loop which required re-operation. She survived and remains relieved of the symptoms of hernia and ulcer. She has occasional bouts of gallstone colic.

One patient was known to have recurring pancreatitis which had been demonstrated at a previous operation. On her third postoperative day, she had an attack of acute pancreatitis which was very severe, but recovery followed conservative management. The patient now has no symptoms referable to her hernia, but complains of fat intolerance and epigastric pain radiating to the back. She has since had a section of the sphincter of Oddi, with considerable subjective improvement.

One patient complained of severe and persistent chest pain and had some intercostal nerves resected by the neurosurgical department without benefit. He was considered for more radical

measures, but on the advice of the psychiatrists these were deferred. When seen five years after operation, his gastro-intestinal complaints were minimal, but he still complained of some pain in his scar, which was not severe and was described as constant and aching.

Hospital Stay

TABLE VIII.
Average Days in Hospital Postoperatively

DVA	24.7; 1 patient—61 days
Private	19.0; 1 patient—51 days 1 patient—43 days

The average number of days in hospital after operation was 24.7 in Deer Lodge Hospital and 19 in the private series. One patient with a severe wound infection remained in Deer Lodge for 61 days, and raised the average stay considerably. The two patients in the private series who remained for 51 days and 43 days were those who developed acute pancreatitis and intestinal obstruction respectively.

Follow-up

TABLE IX.
Duration of Postoperative Follow-Up

5 years	1 patient
4 "	3 patients
3 "	5 "
2 "	5 "
1 "	4 "
Less than 1 year	6 "

All the patients have been followed up to the present date (June 1, 1956). The duration of follow-up is as shown in Table IX.

Results

TABLE X.—Results

	Immediate	*Late*
Good	23	18
Fair	1	5
Poor	0	0
Reccurrence	0	0
Died	0	1

In the immediate postoperative period, i.e. three to six months, all the patients except one had a good result. By this is meant that there was no evidence of recurrence of the hernia as judged by barium series, the patients were relieved of their symptoms of reflux œsophagitis, were able to eat without difficulty, and felt that the operation was worth while. In the survey to date, there were considered to be five fair results, which include the one patient mentioned as having a fair result in the immediate postoperative period. There were no poor results, and no evidence of recurrence. One patient has since died of unknown causes two years after operation.

The five fair results were all in patients who had presented problems in the decision about operative treatment. The first of these was considered to have a fair result in the immediate postoperative period. He was an active RCAF man, aged 27, whose complaints were classical and most bitter, who failed to respond to months in hospital on strict postural, dietary and drug therapy, and who presented evidence of œsophagitis, leukoplakia and ulceration at the cardia. After operation, he complained of burning epigastric pain which was persistent, aggravated by food and not relieved by bed rest, Sippy diet, anticholinergic drugs or sedation, for a period of six months. He also complained of severe pain in his chest. Eventually he had a subtotal gastric resection which relieved his complaints, and when seen five years after operation, had no complaints of regurgitation, could sleep flat without distress, and was on a full diet with the exception of condiments and spicy foods. He still complained of some chest pain.

One patient developed severe pulmonary sepsis postoperatively, and now shows some pulmonary fibrosis and complains of shortness of breath. He has no regurgitation, has gained a large amount of weight, and complains of occasional heartburn relieved by antacids.

The third patient rated as having a fair result had had multiple operations for abdominal conditions, but presented a classical story and had medical treatment of various kinds for three years. She was tense and difficult to assess from a psychological point of view. However, she had a hiatus hernia with moderate œsophagitis. Incidentally, barium series did not show the hernia. Her immediate postoperative course was uneventful, but she has since been seen many times complaining of indigestion and fat intolerance, burning epigastric pain and chest pain. There is no evidence of recurrence, she has no symptoms of reflux, and œsophagoscopy reveals no œsophagitis. Repeated investigation reveals no organic cause for her complaints.

She is being treated by a psychiatrist for her tension and emotional instability.

The remaining two patients who are rated as fair results had active duodenal ulcers. In addition to abdominal pain they had definite reflux œsophagitis, and a sliding hiatus hernia was demonstrated radiographically. Their immediate response to operation was excellent, but on recent review both complain of occasional reflux when they have committed some dietary indiscretion, and of heartburn and epigastric pain. Œsophagoscopy shows no œsophagitis, and barium series shows no recurrence of the hernia.

SUMMARY

In this series, which is admittedly a small and statistically insignificant one, the operation devised by Allison has been successful in curing the symptoms ascribed to reflux of gastric contents. No patient has yet developed stricture at the cardia after the operation, but it has not been possible to œsophagoscope these patients routinely some months after operation. We believe that this should be done in order to estimate the degree of cure of œsophagitis. The duration of the follow-up period is too short to make any statement regarding recurrence, but suture of the peritoneal reflection and phreno-œsophageal fascia to the under surface of the diaphragm plus narrowing of the hiatus from behind would appear to give a maximum amount of security in this regard. The operation itself is not shocking; complications are those of associated disease and of opening the chest. No major vessels or viscera are opened or interfered with.

From a technical point of view, exposure of all structures is excellent, sutures can be placed with precision, and the upper abdomen can be explored with ease.

Selection of patients requires considerable care, and it is believed that all patients should have a period of medical treatment before operation is considered. The association of coronary artery disease, duodenal ulcer, gall-bladder disease, and pancreatitis makes it difficult to decide at times which condition demands priority of treatment. The demonstration of a sliding hernia, either by barium series or œsophagoscopy, and the presence of œsophagitis which does not yield to medical treatment, are believed to be essential before operation is recommended.

While the complete mechanism at the cardia is probably not understood, Allison's operation appears to be a rational attempt to restore physiological conditions at the cardia, and observes the principles of hernia repair as carried out elsewhere. In our hands it has so far been satisfactory in relieving the symptoms ascribed to reflux œsophagitis at the cardia.

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RÉSUMÉ

Les symptômes causés par l'œsophagite de régurgitation semblent disparaître après l'intervention d'Allison. Aucun des malades rapportés par l'auteur n'a subi de rétrécissement après avoir été opéré. L'œsophagoscopie nécessaire dans l'évaluation de l'œsophagite ne peut être pratiquée pendant quelques mois après l'opération. La technique de cette opération est physiologique et l'intervention elle-même est habituellement bien tolérée. Le choix des malades doit être fait avec soin. Il est souvent difficile de savoir lequel des états associés doit être traité le premier. L'indication repose sur la démonstration radiologique d'une hernie diaphragmatique avec glissement et sur des symptômes d'œsophagite confirmés si possible par l'œsophagoscopie et rebelles à toute thérapeutique médicale.

CLINICAL EXPERIENCE WITH G-23350 (SINTROM)*

R. JOHNSON, M.D., A. DAVID, M.D. and Y. CHARTIER, M.D., *Montreal*

RECENT PUBLICATIONS made us aware of a new synthetic anticoagulant, nitrophenyl-acetyl-ethyl-4-oxycoumarin, introduced for clinical investigation purposes under the name of G-23350 or Sintrom.† We are presenting the results and conclusions of our study of this drug on 50 patients.

Sintrom is a synthetic anticoagulant of the coumarin group, thus resembling chemically dicoumarol and ethyl biscoumacetate (Tromexan) and having the same action in inhibiting synthesis by the liver of prothrombin and of factor VII (convertin). The final mechanism of their action is a competitive interference between these drugs and vitamin K in the hepatic cell.

*Work done in the Department of Medicine, Section of Cardiology, Notre-Dame Hospital, Montreal.
A French version of this study appeared in *L'Union Médicale*, **86**: 408, 1957.

†Sintrom was supplied by Geigy Pharmaceuticals.

MATERIAL AND METHOD OF STUDY

Sintrom was administered to 50 patients suffering from a pathological condition where anticoagulants seemed to be indicated. These cases were classified as follows:

A—recent myocardial infarction:
18 cases (12 men, 6 women)
—without complications: 11
—with arrhythmias: 4
—with cardiac failure: 3
—with shock: 3
—with peripheral arterial embolism: 1
—associated with pulmonary embolism: 1
—associated with hyperthyroidism: 1
—associated with atrophic cirrhosis: 1
(In the cases of embolism, treatment with anticoagulants was started after the onset of the pathological condition.)

B—Coronary insufficiency: 13 cases (9 men, 4 women)
—with a past myocardial infarct: 7
—without a past myocardial infarct: 6

C—Rheumatic heart conditions with arrhythmia (auricular fibrillation): 13 cases (5 men, 8 women)
—with cardiac failure: 8
—with pulmonary embolism: 3
—associated with hyperthyroidism: 3

D—Thrombophlebitis of the limbs:
3 cases (2 men, 1 woman)
—associated with a past myocardial infarct: 1
—with secondary pulmonary embolism: 1
(In the latter case, the embolism preceded the use of anticoagulants).

E—Miscellaneous: 3 cases (3 men)
—Thrombosis of the internal carotid with cardiac failure: 1
—Stokes-Adams syndrome: 1
—fracture of the tibia in an elderly patient with advanced varicosities of the legs and past history of many attacks of thrombophlebitis: 1

The series thus included 31 males and 19 females. Their age ranged from 33 to 77 years and their weight from 110 to 220 lb.

We have taken into account factors which may have modified the action of the drug (such as intestinal absorption, utilization, elimination, and simultaneous ingestion of certain other drugs), and we shall refer to this in the interpretation of certain results.

Sintrom is available in white tasteless tablets of 4 mg.

The daily amount of prothrombin was determined by the one-stage method at the bedside, consisting in taking 0.7 c.c. of venous non-citrated blood and 0.1 c.c. of thromboplastin, and timing exactly the appearance of the clotting in the tube (Howell). The result, obtained in seconds, is converted to a percentage. We consider as the best therapeutic level, in agreement with the criteria already established by many authors, a blood clotting time prolonged to at least 2½ times the normal. According to our method, which has no connection with the Quick method or its modifications as regards expressing the results, this effective therapeutic level is below 40%. (When we reach 20%, for example, the clotting time is 4 to 5 times shorter than normal, which is considered as being 80 to 100%.)

RESULTS

1. What is of primary importance to us is the rapidity in obtaining a therapeutic level with this drug. When the initial prothrombin level is normal, that is, between 80 and 100%, it is unlikely, except in very rare instances, that a level of 40% can be reached in less than 24 hours. However, with sufficient doses, one can in almost all cases obtain this therapeutic level in 48 hours or less (Table I).

TABLE I.

		Therapeutic level obtained in:		
Case	*Total number*	*48 hours or less*	*48 to 72 hours*	*Exceptions*
Group A	18	14	4	——
Group B	13	8	4	1 case - 7 days
Group C	13	9	3	1 case - 4 days
Group D	3	2	—	1 case - 7 days
Group E	3	2	1	——
Total	50	35	12	3

Of the 50 cases, it was possible to reach a therapeutic level within 48 hours in 35 cases (70%). It is seen that this number could have been greatly increased if we analyzed the 15 cases in which the level was not reached; in nine cases, at the beginning of the study, our initial dosage was inadequate in the light of further experience. The six other cases represented, however, examples of "resistance" to the drug, or unpredictable individual response. In the light of this, we believe that in 85% to 90% of cases a therapeutic prothrombin level can be achieved in at least 48 hours.

2. *Initial dosage:* What then is the initial dose to be given in order to obtain this effective therapeutic level? It varies, of course, according to the initial prothrombin level. To try to determine this dose, we have measured the rate of fall in prothrombin level obtained in the first 24 hours with different doses, in cases with a normal prothrombin level at the start of treatment (Table II).

Table II shows that with doses of 20 to 28 mg. the most frequent fall in the prothrombin level is between 20 and 40% (25 cases out of 28) but with extremes ranging from 9 to

TABLE II.

Initial dosage	*Number of cases*	*Intensity of lowering in the first 24 hours*					
		10% or less	*11 to 20%*	*21 to 30%*	*31 to 40%*	*41 to 50%*	*51 to 60%*
28 mg. (7 tablets).....	20	1	0	9	6	1	3
24 mg. (6 tablets).....	8	0	2	2	3	0	1
20 mg. (5 tablets).....	10	0	1	5	0	3	1
Total.....	38	1	3	16	9	4	5

65%. Thus it is also evident that the individual initial response is variable and unpredictable. We will study later the possible causes of certain abnormal reactions. On the other hand, in cases which at the start of treatment have a prothrombin level of 80% or more, doses of five to seven tablets (20-28 mg.) are never dangerous, even in cases of "sensitiveness" to the drug. More care is needed if the prothrombin level is low at the start, and therefore the second dose will have to be adjusted according to the response obtained in the first 24 hours.

3. *Maintenance dosage:* Keeping in mind the circumstances (pathological conditions or idiosyncrasies) which have been factors in the rate of fall in prothrombin level during the first 24 hours, the subsequent and maintenance daily doses should be, according to our experience, as follows:

	Tablets
for a prothrombin level between 60 and 80%:	4 to 6
for a prothrombin level between 40 and 60%:	3 to 5
for a prothrombin level between 30 and 40%:	2 to 3
for a prothrombin level between 20 and 30%:	½ to 2
for a prothrombin level lower than 20%:	0 to ½

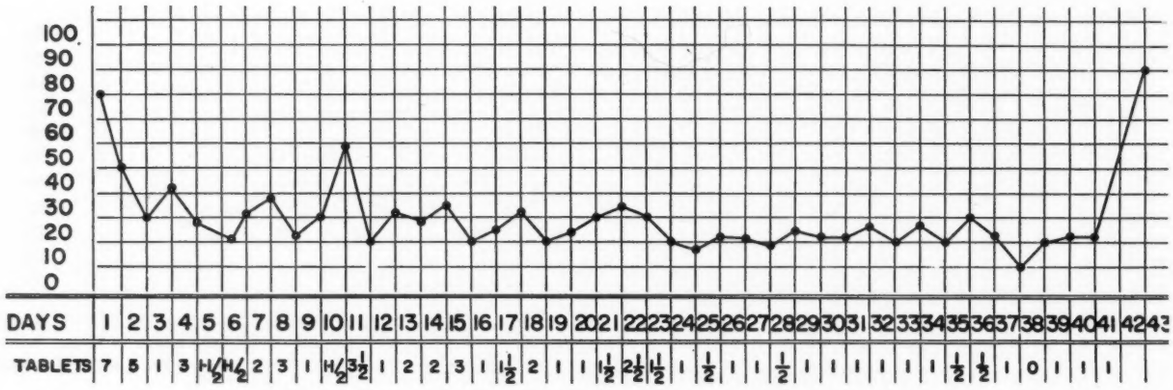

Fig. 1.—P.L. Case 32. Mitral disease, multiple pulmonary embolism.

4. *Stabilization of the prothrombin rate at the therapeutic level:* Most of our cases were treated for periods of 10 to 40 days. With the

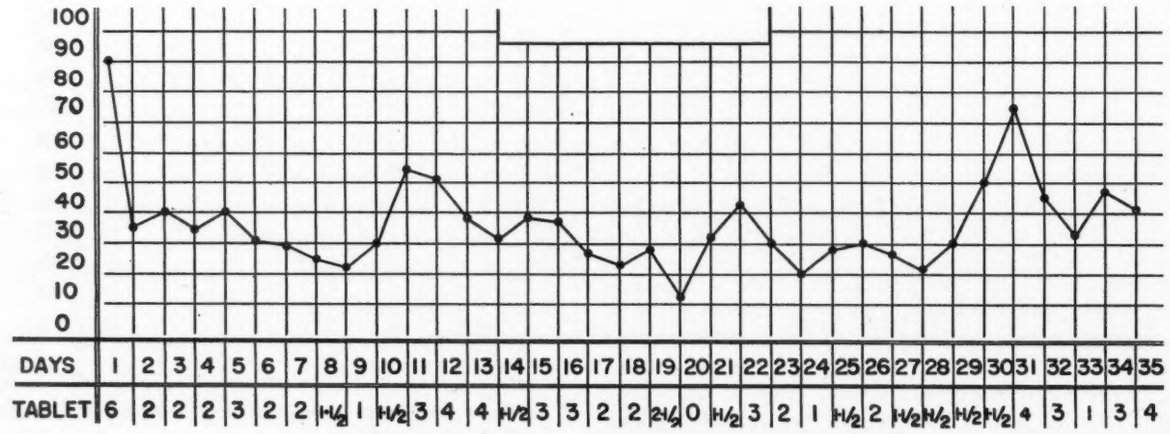

Fig. 2.—C.D. Case 15. Myocardial infarction.

maintenance dose and daily control of the prothrombin level, it is relatively easy to keep the prothrombin level quite stable without too much variation above the therapeutic level (Figs. 1 and 2). This lower frequency of unexpected and high rises with Sintrom is a marked advantage over Tromexan. On the other hand, with Sintrom, as with all other anticoagulants, it is preferable to test the prothrombin level every day when the patient is in hospital. However, once the patient is well stabilized, it is possible to maintain the desired level well enough without daily tests, and Sintrom can be continued, as we have effectively done, with the patient at home, with spot checks of the prothrombin level.

5. *Duration of action, accumulation and return to normal after cessation:* It was shown previously by one of us[1] that the drug action begins approximately eight to 12 hours after its administration, reaches its maximum after about 24 hours, is maintained for about 24 hours, and progressively disappears in the following 24 to 48 hours.

It has no notable cumulative effect; if a dose is omitted one day, the prothrombin percentage will not fall the next day.

In the 25 cases in which it was tested, the return to normal of prothrombin level, after the drug was stopped, took place in 24 cases in 72 hours or less. In the other case, this return took place in 96 hours.

6. *Resistance to the drug:* We speak of "resistance" when the initial lowering of prothrombin level in the first two days is weak with the usual doses, when the maintenance dose is above the usual dose, and when return to normal is very rapid after the drug is stopped. Excluding the obvious causes of malabsorption of the drug, notably vomiting and diarrhœa, we have no explanation to give for this resistance.

In our series, we encountered one case of marked resistance (Fig. 3) where it was difficult with large doses to reach the therapeutic level and where the maintenance doses used were about twice the doses previously suggested. We consider six other cases as being "slightly resistant", that is, the maintenance doses required were in general 2 to 4 mg. above the usual dosage (Fig. 4).

With Sintrom as in general with all drugs there is no fixed ruling as far as dosage is concerned, even when all the known factors of variation in effect have been considered.

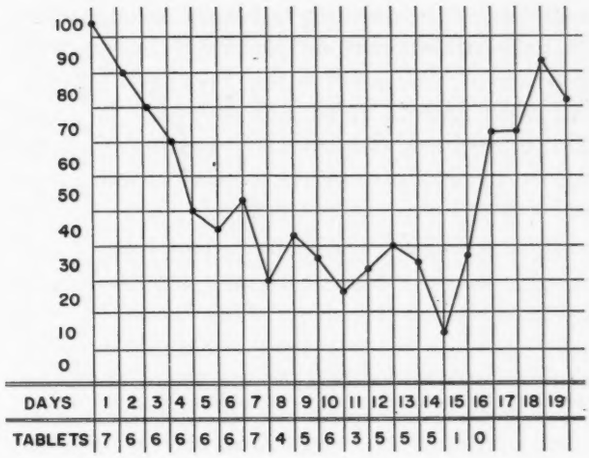

Fig. 3.—M.B. Case 21. Coronary insufficiency.

7. *Sensitiveness to the drug:* We speak of "sensitiveness" or of a greater susceptibility to the drug when, with the usual dosage, the initial fall is exaggerated, when the maintenance dosage is less than usual and the return to normal is very slow after cessation of administration.

Many factors may make a patient "sensitive" to an anticoagulant. Age, sex or weight did not seem to have any bearing here. On the other hand, it is reasonable to think that an enlarged liver in a patient with cardiac failure and a pre-treatment prothrombin level at 65% is unable to synthesize the prothrombin at a normal rate; or that again the administered drug may be slowly eliminated, as in certain cases of renal deficiency with oliguria. In these last two

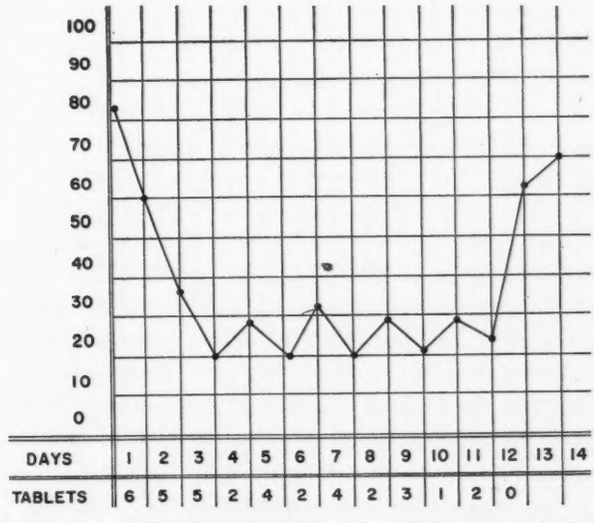

Fig. 4.—M.D. Case 41. Mitral insufficiency, auricular fibrillation.

examples it is possible, up to a certain point, that the patient may be "sensitive" to the drug; a practical conclusion is that one must be careful what dose is given and be ready to adjust the dose from day to day according to the response, which may be variable and often differs from one day to another.

In our series eight patients (one given anticoagulants on three occasions) can be classed as sensitive to the drug. This sensitivity was very marked in two cases (Fig. 5), less or slightly marked in the others; six of these patients had cardiac failure with congestive hepatomegaly, and two other patients had a renal deficiency pronounced enough to alter renal function tests significantly.

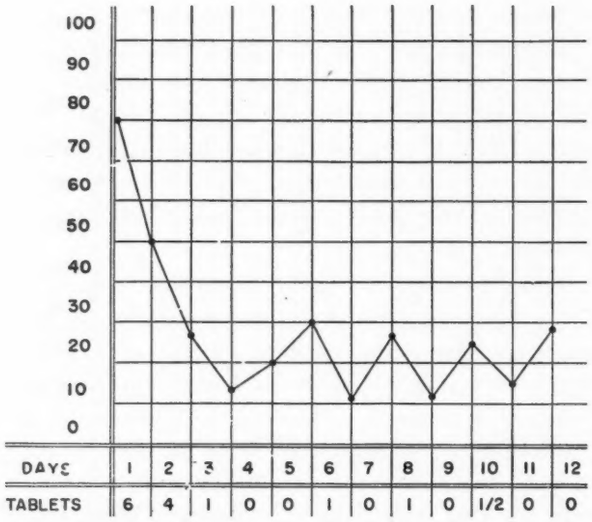

Fig. 5.—J.R. Case 49. Cardiac insufficiency, internal carotid thrombosis.

Lastly, it seemed to us that certain drugs administered concurrently could modify the reaction to anticoagulants, and lead to a greater sensitiveness.

(a) *Chlorpromazine* (*Largactil*). Out of eight cases where it was administered concurrently, in daily doses ranging from 40 to 100 mg., chlorpromazine seems to have played a slightly sensitizing role in two cases. We mention this because it is possible that in larger doses this effect could be more marked. This action may be due to the "narcobiotic" activity of chlorpromazine; that is, its property, as with all phenothiazine derivatives (antihistamines, antiparkinsonians, etc.), of slowing the activity of living cells, including the hepatic cell.

(b) *Broad-spectrum antibiotics:* The majority of diets contain a sufficient amount of natural vitamin K absorbed from the intestine when bile is present. Moreover, the intestinal flora synthesizes it from the ingested food, thus making it impossible for the body to have a deficiency of vitamin K, save when the latter does not reach the liver, since it is not absorbed because of a blockage of the bile ducts. Hence an anorexic patient taking bacteriostatic drugs will probably be more sensitive to coumarin agents.

In the course of treatment, three of our patients have taken chloramphenicol (Chloromycetin); in one case, the antibiotic seems to have been one of the causes of greater sensitivity to the anticoagulant.

(c) *Aspirin:* It is known that salicylates have a hypoprothrombinæmic action. The mechanism is probably also a blockage of utilization of vitamin K in the hepatic cell, as with the coumarins. Even if this action is rare with doses below 6 g. a day, it is recommended as a general rule not to give aspirin concomitantly with the coumarins, the addition of these two drugs theoretically accentuating hypoprothrombinæmia. Yet certain authors[2] have demonstrated on the contrary that salicylates—maybe by being broken down to certain products whose chemical formula is related to dicoumarol—may inhibit the action of the latter, always by the same theoretical competitive phenomenon, and consequently lessen the hypoprothrombinæmic effect of coumarins. This means that theoretically salicylates may lessen or increase the effect of coumarins.

This fact is mentioned because in five cases we have not been able to demonstrate these actions one way or the other; it is true that all these patients were taking less than 3 g. of salicylates per day.

8. *Accidents and toxic effects*: We have encountered in our series two cases of macroscopic hæmaturia, one with a prothrombin level of 14% and the other with a prothrombin level of 20%. This last one only was serious enough to necessitate giving vitamin K (Mephyton), and 12 hours after the administration of 50 mg. i.v. the prothrombin level had gone up to 94% and the hæmorrhage had stopped. In these two cases, the hæmorrhagic accidents had no serious consequences. We should also report a hæmoptysis of about 800 c.c. that occurred with a prothrombin level of 8% in a patient who for 12 hours had been in an irreversible state of acute pulmonary œdema and was dying. Hence

there were three accidents, and one was one of the causes of death. We attribute these accidents to the inherent risk of all anticoagulant therapy.

On the other hand, we have not observed any untoward or toxic effect of the drug on any system or organ. Gastro-intestinal tolerance is excellent.

SUMMARY

Our clinical experience with Sintrom allows us to draw the following conclusions:

The action of this anticoagulant is rapid; in 70% of our series of 50 cases, the therapeutic level was reached in 48 hours or less. With our present experience in the use of Sintrom, we believe that this therapeutic level could be attained in 48 hours or less in 85 to 95% of cases.

With initial doses varying between 20 and 28 mg. (5 to 7 tablets), the prothrombin time is lowered in the majority of cases to 20 and 40%. With these initial doses, we have never obtained a fall to a dangerous level, even in cases considered as "sensitive" to the drug. The subsequent doses are unpredictable and require daily adjustment. Our experience enables us to recommend "theoretical" doses which, in the great majority of cases, lower the prothrombin time to a therapeutic level in the first 48 hours and maintain this level for the duration of treatment.

Sintrom has no cumulative effect and its effect disappears in the 72 hours after the last dose of the drug.

There exist cases of resistance to the drug and also cases of sensitiveness. As with the other anticoagulants, one must be aware of the synergistic action of certain drugs such as salicylates, and the inhibitory action of vitamin K and certain other drugs such as broad-spectrum antibiotics.

The few hæmorrhagic accidents which occurred in this series cannot be attributed to Sintrom *per se;* these mishaps also occur as frequently with other anticoagulants.

Sintrom has the advantages over Tromexan of possessing a more predictable action and being easier to give (one daily dose only). It does not have the cumulative effect of dicoumarol, thus lowering the danger of prolonged hæmorrhagic accidents.

With Sintrom as with other anticoagulants, the response remains an individual one, often unpredictable, and necessitates a daily determination of the prothrombin time. However, when the individual response is well known, it is possible to administer the drug over a long period with weekly or twice monthly control of prothrombin time.

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REHABILITATION IN TUBERCULOSIS
A SEVEN- AND EIGHT-YEAR FOLLOW-UP

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A PREVIOUS REPORT[1] was made on 326 veterans who had been discharged from Western Counties Veterans' Lodge, Department of Veterans Affairs, London, Ontario. There were two groups: 160 veterans discharged by the end of December 1948, and 166 discharged during the calendar year 1949. These groups may be considered as belonging to the pre-chemotherapy era.

The first report was a two-year and one-year follow-up since discharge from the Rehabilitation Centre. This one is an eight-year and seven-year follow-up respectively, the records being reviewed in June 1956.

The last medical examination for the 326 veterans was done within three months of the review for 31% of the veterans, and within five months, or during 1956, for 53%. Another 35% were examined between six and twelve months ago. Most of the patients are on one-year follow-up examinations but some are on two-year examinations. Twenty-one were dropped from the routine follow-up: four in 1951, six in 1952 and 11 in 1953 and early 1954. The 21 men and another 19 examined between 13 and 24 months ago make up the remaining 22%. In all but three persons there was evidence on file that they were still in contact with DVA for reasons other than medical. Through such means it was possible to determine within a period of six months to two years whether or not they were working.

In review, terms used are explained as follows:

Direct admissions—those men who entered the centre by a direct transfer from sanatorium or had a period of not more than three months on leave or out-patient status before entering the Lodge.

TABLE I.—Eight-Year Follow-Up Since Discharge From the Centre (or About 9 Years Since Discharge from Sanatorium): 160 Men Discharged as "Well" by December 31, 1948

Disease classification	*No. of men*	*No. of reactivations*	*Number well and working*	*Number well but not working*	*No report or no trace*	*Deaths TB.*	*Deaths Other*	*Not fit In San.*	*Not fit Out-patient*	*Not fit Other institution*
Pleurisy with effusion...	13	3	13	—	0	0	—	0	—	—
Disseminated T.B. including bilateral pleurisy with effusion	3	0	3	—	0	0	—	0	—	—
Pulmonary T.B. minimal	53	15	47	2	0	0	1**	0	3	—
Pulmonary T.B. moderately advanced	69	10	64	3	0	0	1**	0	—	1
Pulmonary T.B. far advanced.....	17	0	17	—	0	0	—	0	—	—
Extrapulmonary.....	5	1*	5	—	0	0	—	0	—	—
Total.....	160	29	149	5	0	0	2**	0	3	1
Percentage.....	100%	18.13%	93.13%	3.13%		—	1.25%	—	1.87%	0.62%
Percentage at the two year follow-up.....	11.30%	80.00%	6.3%	1.20%						

* Two were reported previously. One was proven to be inactive after two months' investigation.

**Both deaths were due to suicide. Each man had been examined within six months of death—no active T.B.

Indirect admissions—those who had a longer period than three months.

Complete graduates—those who remained long enough to reach an exercise tolerance considered equivalent to their immediate full day of employment or study at school or college.

Incomplete graduates—considered fit for part-time employment or school work and having a goal in mind.

Undergraduates—incomplete graduates and others who left the centre after a brief stay and had no particular goal in mind. Those who presented disciplinary problems are included.

Discharged as "well"—regardless of the number of days' stay or rehabilitation status at the time of discharge, there was no clinical reason for the patient to be treated in sanatorium. However, a recommendation might have been made to the effect that he required close supervision as an out-patient.

Tables I and I-A include all classes described above. The duration of stay at the centre ranged from seven days to 681 days.

TABLE IA.—Seven-Year Follow-Up Since Discharge Feom The Centre (or About 8 Years Since Discharge From Sanatorium): 166 Men Discharged as "Well" During Calendar Year 1949

Disease classification	*No. of men*	*No. of reactivations*	*Number well and working*	*Number well but not working*	*No report or no trace*	*Deaths T.B.*	*Deaths Other*	*Not fit In San.*	*Not fit Out-patient*	*Not fit Other institution*
Pleurisy with effusion...	3	—	3	—	—	—	—	—	—	—
Disseminated T.B. including bilateral pleurisy with effusion	6	—	6	—	—	—	—	—	—	—
Pulmonary T.B. minimal	33	3	30	1*	2*	0	0	—	—	—
Pulmonary T.B. moderately advanced	86	14	82	—	3**	—	—	—	1	—
Pulmonary T.B. far advanced.....	35	6	29	1*	2	—	—	—	2	1
Extrapulmonary.....	3	—	3	—	—	—	—	—	—	—
Total.....	166	23	153	2	7	0	0	0	3	1
Percentage.....	100%	13.85%	92.17%	1.21%	4.21%		—	—	1.81%	0.60%
Percentage at one year follow-up.....		5.4%	80.1%	9.1%	3.6%	—	—	—	—	—

*One patient with psychopathic personality and one with minimal disease never worked steadily.

**Two were reported working 1952; one no record available at time of study. The patients with minimal disease were non-pensioners and dropped out of touch early.

TABLE II.—STUDY OF REACTIVATIONS AMONG THOSE ADMITTED DIRECTLY AND WHO HAD REQUIRED ONLY ONE ADMISSION TO SANATORIUM PRIOR TO ADMISSION TO THE CENTRE. EIGHTH YEAR POST-CENTRE FOLLOW-UP (AVERAGED NINE YEARS POST-SANATORIUM).

1948 group	*Graduates fit full day* Number	React.	*Undergraduates fit half day or less* Number	React.	*Total* Number	React.
Pleurisy with effusion	8	2	2	1	10	3
Disseminated tuberculosis including bilateral pleurisy with effusion	0	0	0	0	0	0
Pulmonary T.B. minimal	20	3	6	5*	26	8
Pulmonary T.B. moderately advanced	25	3	22	4	47	7
Pulmonary T.B. far advanced	2	0	9	0	11	0
Others	0	0	0	0	0	0
Total	55	8 (14.5%)	39	10 (25.6%)	94	18 (19.2%)***
Average number days at Centre	259	257**	104	133		

*One with inactive pulmonary T.B. but developed new T.B. cervical adenitis.
**There were only two in this group whose stay at the Centre was above the average for complete graduates in the first (1948) group. The average for the remainder was 239 days.
***At two-year follow-up was 10.6%.

The relapse rate has risen from 11.3% (at two-year follow-up) to 18.13% in the eight-year follow-up of the 1948 group and from 5.4% (at one-year follow-up) to 13.85% in the seven-year follow-up for the 1949 group. There are 92.6% considered to be working among the total of the two groups. There are 3.1% at present not well enough to work, but employed between readmissions. This suggests that the rehabilitation efforts on the part of those responsible are reaching better than 95% of their goal.

In such a study it is difficult to explain the variations in the lower relapse rate for the 1949 group. Since the latter group has passed the seventh year and since the 1948 group showed less than 1% new readmissions in the seventh year, have we reached a final percentage at about the 14% mark?

The importance of the time element was suggested in the earlier report. It was stated that the average duration in days at the centre for the 1948 group was 222 days compared with 265 days for the 1949 group. We have evidence of a lower rate in the latter group.

Tables II and II-A represent an attempt similar to that made in the previous report to bring out the importance of time in the treatment of tuberculosis. However, had we been able to treat the individual psychological aspect adequately and give adequate treatment to what may be termed psycho-social problems, there might have been even better results.

TABLE II-A.—STUDY OF REACTIVATIONS AMONG THOSE ADMITTED DIRECTLY AND WHO HAD REQUIRED ONLY ONE ADMISSION TO SANATORIUM PRIOR TO ADMISSION TO THE CENTRE. SEVENTH-YEAR POST-CENTRE FOLLOW-UP (ABOUT EIGHTH YEAR POST-SANATORIUM).

1949 group	*Graduates fit full day* Number	React.	*Undergraduates fit half day or less* Number	React.	*Total* Number	React.
Pleurisy with effusion	1	0	0	0	1	0
Disseminated tuberculosis including bilateral pleurisy with effusion	3	0	2	0	5	0
Pulmonary T.B. minimal	4	0	8	1	12	1
Pulmonary T.B. moderately advanced	36	4	21	4	57*	8
Pulmonary T.B. far advanced	14	1	9	2	23*	3
Others	2	0	0	0	2	0
Total	60	5 (8.2%)	40	7 (17.5%)	100	12 (12%)
Average number days at Centre	350	263	150	160		

*80% of patients in this group had moderately advanced and far advanced pulmonary T.B. while 60.1% of patients in 1948 group had moderately advanced and far advanced pulmonary T.B.

Each of the 52 patients classed as reactivated has been listed and numerous tabulations made. Space does not permit presentation of such detail. Comparisons have not been made with the whole group. There were 18 reactivations among the minimal-disease group. Six had an associated pleurisy with effusion and one of these also had bilateral disease. Two others had bilateral disease; in two cases a pneumothorax was abandoned because of fluid and in one it was unsuccessful because of pleural involvement; three had more than one admission to sanatorium before admission to the centre and one of these had known tuberculous bronchitis; one had multiple calcified tuberculous hilar glands, any one of which could cause future trouble; one was an alcoholic; two had apparently simple unilateral minimal pulmonary tuberculosis.

Among the moderately advanced cases (24 patients altogether) 11 were bilateral, another had disseminated sclerosis and another paresis of the right lower limb due to an old gunshot wound.

Notes made at time of discharge for 19 of the 52 varied as follows: disciplinary discharge; must go cautiously, very active here; fluid in pneumothorax space may lead to complications; thoracoplasty does not give much collapse or thoracoplasty would give better protection, and so on. Actually, six of these patients were classed as having disciplinary problems and several left early for compassionate reasons.

Pneumothorax and Thoracoplasty

Thoracoplasty and pneumothorax cases in the 1949 group were reviewed briefly. There were 31 patients with thoracoplasty, and seven reactivations occurred among these (22.6%). Two reactivations occurred under the thoracoplasty (6 and 7 ribs), and four occurred on the contralateral side (4, 5, 6 and 9 ribs); there was one in which the side of reactivation was not noted.

Forty-nine patients left the centre with their pneumothorax maintained, six with a bilateral pneumothorax. Eight (16%) of these developed extension or relapse. However, only two of the eight had developed reactivation after discontinuing the pneumothorax; the other six were still receiving refills. Excluding the eight reactivations, there were 41 patients carrying 44 pneumothoraces. The average duration of maintaining the collapse was 4.5 years, ranging from 3 to 8 years. In the far advanced cases pneumothorax was maintained for an average of only 4.7 years. One person with minimal pulmonary tuberculosis had the pneumothorax continued for 8 years.

While it was stated that these groups represent patients treated in the pre-chemotherapy period, there were two in the 1948 group and 14 in the 1949 group who received streptomycin only. A dose of either 1 or 2 grams daily for 30 to 60 days was given, except in one case treated for 87 days and another for 199 days. There were two reactivations among

TABLE III.—Year of First Relapse, after Discharge from Centre.
Including all Reactivations in Both Groups.
1948 group without parentheses—1949 group within parentheses

Classification of disease	*Readmissions number of men*		*Year during which relapse or new disease found*						
			First	*Second*	*Third*	*Fourth*	*Fifth*	*Sixth*	*Seventh*
Pleurisy with effusion	3	(0)	2	0	0	0	1	0	0
Disseminated tuberculosis including bilateral pleurisy with effusion	0	(0)	0	0	0	0	0	0	0
Pulmonary T.B. minimal	15	(3)	3 (2)	2	3**	1 (1)	1	4***	1
Pulmonary T.B. moderately advanced	10	(14)	6 (4)	2 (7)	0 (1)	0 (1)	1 (1)	1	0
Pulmonary T.B. far advanced	0	(6)	0 (3)	0	0 (1)	0 (1)	0	0 (1)	0
Other	1*	(0)	0	0	0	0	0	1	0
****Totals	29	(23)	11 (9)	4 (7)	3 (2)	1 (3)	3 (1)	6 (1)	1
	52		20	11	5	4	4	7	1

*Had 3 admissions prior to coming to Centre and several after discharge. All admissions for T.B. cervical adenitis.
**In 2 of these the pulmonary lesions remained inactive—one developed genito-urinary T.B.; the other had 2½ months' hospitalization for T.B. cervical adenitis.
***One showed no change in pulmonary T.B. but developed T.B. ischiorectal abscess.
****31 or 60% reactivated within 2 years.
44 or 85% reactivated within 5 years.
8 or 15% reactivated after 5 years.

these patients. One had recurring tuberculous adenitis (cervical) and the other with far advanced disease took a disciplinary discharge.

It does not seem right to omit a table showing the follow-up year during which first reactivations occurred. Table III and the footnotes are self-explanatory.

TYPES OF EMPLOYMENT

Every type of employment or occupation has been entered by these veterans, and of course many of the previously single men are married and raising families. Among representatives of many vocations are unskilled and skilled labourers, office workers from clerks to office managers, journalists, commercial artists, watchmakers, jewellers, instrument mechanics, mechanics and machinists, lumber scalers and foremen of camps, salesmen and real estate agents, school teachers, ministers, several classes of engineers, lawyers, and doctors. One veteran who had far advanced disease, with bilateral pneumothorax, long discontinued, is in England studying for his Ph.D. in nuclear physics. More detailed study of this subject would be interesting.

The change in treatment today is noted, where, for a few selected cases, combination chemotherapy is continued during convalescence and even when some patients return to work. No one would have guessed four years ago that this chemotherapy would take on the same pattern as maintained pneumothorax therapy did.

SUMMARY AND CONCLUSIONS

A seven- and eight-year follow-up of veterans treated for tuberculosis in the pre-chemotherapy era has been presented. No attempt has been made to compare this with other studies.

1. Treatment has changed so much in recent years that conclusions in the previous report may be obsolete.

2. For persons similarly treated, the relapse rate used to be 25 to 35%. The rate for these groups was under 20%.

3. Again it may be stated that with time and adequate treatment, which includes rehabilitation, any type of employment is possible, even for those treated before chemotherapy was available.

4. The majority of relapses occurred within two years, but follow-up beyond five years is recommended.

5. The time factor, as far as duration of sanatorium care and convalescent care is concerned, may still be considered one of the most important factors, at least for these pre-chemotherapy groups.

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ANALYSIS OF ADMISSION CHEST RADIOGRAPHS AT ST. ANTHONY HOSPITAL FOR THE YEAR 1955*

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INTRODUCTION

THE VALUE of routine admission chest radiographs for all patients admitted to a general hospital has been appreciated for over thirty years, but practice of this routine is by no means universal. This paper analyzes the findings in such a program at St. Anthony Hospital during the year 1955.

*Presented at meeting of Newfoundland Medical Association, St. John's, Newfoundland, September 10, 1956.

PREVIOUS LITERATURE

There have been numerous studies concerning the prevalence of tuberculosis in patients admitted to a general hospital. A few of the findings have been selected for comparison with the present study.

1. 1935: Hodges studied the findings in the radiographs of 1101 patients at the University of Michigan Hospital; 1.3% had significant chest disease unrecognizable by other methods of examination.[1]

2. 1940: Plunkett and Mikol surveyed radiographs of 4853 patients admitted to general hospitals in upstate New York; 2.6% had evidence of the reinfection type of tuberculosis and 1.1% had clinically significant lesions.[2]

3. 1945: Epstein and Meliss surveyed 3487 admission radiographs in a private hospital in New York; 3.2% had a reinfection type of

tuberculosis; 0.6% had active tuberculosis; 0.37% were not suspected before radiography.[3]

4. The radiographs taken during the first two years of such a program in several hospitals in New York State were studied from 1947 to 1949; 1.13% had significant lesions; 0.25% were proven to have active tuberculosis.[4]

5. In a study of approximately half a million veterans admitted to hospital 2.42% were diagnosed as tuberculous; 0.8% were proven to have active tuberculosis.[5]

6. In 1954 Jacobson and Alder reported on the first year of routine admission chest radiographs at the Los Angeles County Hospital. Of a total of 49,578 patients, a final diagnosis of tuberculosis was made in 2.1%; 1% were proven to have active tuberculosis.[6]

In some of the above studies, diagnosis of tuberculosis was made on patients previously known to be infected. The purpose of the present study is to emphasize the value of x-raying patients who otherwise would not have been x-rayed.

PROCEDURE AT ST. ANTHONY

Routine admission radiographs have been taken at St. Anthony since June 1954, as recommended by the Joint Commission on Accreditation of Hospitals.

All patients admitted during the previous 24 hours are checked every morning and x-rayed if that has not already been done. The ideal would be to x-ray each patient on admission, but this was soon found to be impractical for reasons outlined below.

Most of the radiographs are viewed while they are still in the washing tank, at some time in the afternoon. They are then transferred to the viewing room where they are marked and filed for reporting. Official reports are made on all radiographs once or twice a week, usually by the same member of staff.

There are obvious loop-holes in such a procedure. Adaptations in detail are still being made to cover every admission. It was soon realized that not every patient admitted was being x-rayed. With some dismay, it was discovered that 173 patients, or 13.7% of the total admissions, had missed admission radiography in 1955.

Some of the problems encountered were as follows:

The main problem is shortage of staff. There is one x-ray technician who also has other duties. If he is not available, radiographs must be taken by one of the medical staff of three, one of whom may be away from the station. With a temporary increase in the x-ray staff during the last two months, not more than two or three patients have been missed.

The x-ray room is on the ground floor and most of the patients are on the first floor. The x-ray machine is powered by an independent generator which must be set in operation each time a radiograph is required.

Many of the patients arrive in groups of 15 to 20 on the coastal steamers which often dock during the night.

If there is a shortage of beds in the hospital, patients must be housed in the Annexe, a building separate from the hospital.

Any such program requires the full cooperation of all members of staff.

There are many more minor problems but it should only be a matter of time before such a routine becomes automatic.

During 1955, 1234 patients were admitted to St. Anthony Hospital. This figure includes those admitted to the tuberculosis sanatorium, most of whom were already known to be tuberculous.

Similarly, several patients were referred to St. Anthony specifically for chest radiography and further investigation for possible tuberculosis. All such patients have been excluded from the final analysis.

It is presumed that patients admitted with pulmonary symptoms would have a chest x-ray in the normal course of their investigations. These too have been excluded from the final analysis.

TABLE I.—PRELIMINARY ANALYSIS

Classification	*Newborn*	*Known or suspected tuberculosis*	*Pulmonary symptoms*	*Unrelated symptoms*	*Total admissions*
Number	168	167	45	854	1234
Percentage	13.6%	13.5%	3.7%	69.2%	100%

All newborns are excluded from the final figure.

Only the chest x-rays of patients admitted with symptoms not related to the lungs are included in this case-finding survey.

For the purposes of this survey, those patients who did not have x-rays must be regarded as being negative.

Of the 1234 admissions, 168 were newborn; 167 were known to be tuberculous, or were admitted specifically for investigation of tuberculosis; 45 patients were admitted with pulmonary symptoms, three of whom were later proven to be tuberculous.

Of the 1234 admissions, 854 were admitted with symptoms for which there was no specific indication for chest x-ray.

Analysis of these 854 patients is as follows:

TABLE II.

Classification	*Cardio-vascular disease*	*Cervical ribs*	*Inactive tuberculosis*	*Active tuberculosis*	*Negative chest x-ray*	*Total*
Number	45	3	56	23	727	854
Percentage	5.27%	0.35%	6.56%	2.70%	85.12%	100%

Forty-five patients, or 5.27%, were seen to have abnormalities related to the cardiovascular system. Many of these were admitted with cardiac symptoms.

Three patients, or 0.35%, were found to have cervical ribs which were asymptomatic.

Patients seen to have increased bronchial markings or emphysema, many of whom were old, are not included in this analysis.

There were no cases of carcinoma of the lung.

Fifty-six cases, or 6.56%, were diagnosed as having inactive tuberculosis.

Twenty-three patients, or 2.70%, were considered to have active tuberculosis. Of these 23, eight or 0.93% of the total were proven to be active. Two of these patients refused treatment. One patient was referred to another clinic. Thirteen patients are being followed up. Three of these 13 patients have shown regression of the original lesion and their disease is regarded as being quiescent.

Classification of chest radiograph findings as active or inactive is by no means infallible.

Newell, Chamberlain and Rigler published an interesting paper on a survey they made which they describe as a "revelation of unreliability in the roentgenographic diagnosis of tuberculosis".[7] They dealt with the different diagnoses made by different individuals on reading the same radiographs, and by the same individual on re-reading the same radiographs.

Nevertheless, diagnosis by such means remains the basic standard in surveys of this sort. The advantage of such a survey in a hospital is that patients can be subjected to further investigation if such is thought necessary.

It is interesting to note that one of the patients in the present survey was diagnosed as having inactive tuberculosis on admission radiography. Following subsequent gastrectomy, the patient's disease showed signs of progression, and was later confirmed as being active.

At this point, it would be well to compare similar figures in nearby areas during mass x-ray surveys. Figures for 1950 have been compared with the present survey. Nineteen hundred and fifty was the first year in which mass surveys were made in northern areas. On the south coast of Labrador, of 1576 radiographs taken, 1.4% were diagnosed as showing active tuberculosis. In the Notre-Dame Bay area, of 2579 radiographs taken, 1.13% were diagnosed as showing active tuberculosis.

Similar figures available for mass surveys carried out in 1955 show a very much smaller percentage of active cases found.

DISCUSSION

This paper has been presented to emphasize the value of routine hospital admission radiography as a case-finding factor. The percentage of active cases found has been compared with the number of cases found in a mass x-ray survey in the same and similar areas.

This survey is not concerned with the rate of tuberculosis. It would seem pertinent, however, to make a few observations on this point.

The incidence of tuberculosis is high in Newfoundland as the following figures* indicate.

*From: Tuberculosis Statistics, 1956. Dominion Bureau of Statistics, Health and Welfare Division, Institutions Section, 1957.

PATIENTS UNDER CARE, PER 100,000 POPULATION CANADA, 1954, 1955 AND 1956

	1954	*1955*	*1956*
CANADA	223.2	219.9	200.3
Newfoundland	409.5	412.1	423.3
Prince Edward Island	270.5	203.7	173.2
Nova Scotia	266.9	350.7	360.2
New Brunswick	399.3	389.1	331.6
Quebec	249.6	241.9	234.0
Ontario	153.5	153.1	141.6
Manitoba	295.2	256.3	266.4
Saskatchewan	187.9	181.3	161.5
Alberta	175.0	155.6	163.8
British Columbia	226.4	228.0	193.4

With the limited references available, it has not been possible to make comparisons with a similar survey undertaken elsewhere in Canada.

The relatively crowded and poorly ventilated conditions in which most of the population live would favour spread of the disease. A large-scale attack on the elimination of tuberculosis has taken place only comparatively recently in this area.

It is felt that this survey takes in a good cross-section of the population involved. At no time was there an influx of new cases from any one area.

An analysis by age and sex of the 23 positive cases is as follows:

Age group	*No. of patients*
0 - 10	3
11 - 20	2
21 - 30	5
31 - 40	3
41 - 50	6
51 - 60	2
Over 60	2
Total	23

Sex	*Male*	*Female*	*Total*
No. of patients	9	14	23

It is not felt that these results have any relationship to race. A good proportion of patients admitted here are Eskimo and a lesser number are Indian. The majority are descendents of white settlers on these coasts. The incidence of tuberculosis is high among the native races. However, most of the Eskimo and Indian patients are referred from a more northerly hospital where a diagnosis has already been made. They are therefore not included in the final analysis. A breakdown of some of the figures will illustrate this point. There are of course mixtures of the three races, but each patient has been assigned to the race that is felt to be predominant.

	Eskimo	*Indian*	*White*
167 patients admitted with a previous diagnosis or suspicion of tuberculosis	66	6	95
56 patients diagnosed as having inactive disease	4	0	52
23 patients diagnosed as having active tuberculosis	3	0	20

It may be well to quote the editorial in this year's annual report of the Newfoundland Tuberculosis Association.[8]

"The Department of Health, in co-operation with the Newfoundland Tuberculosis Association, and government and private hospitals, has now finalized plans for a Hospital Admission Chest X-ray programme, whereby every patient entering hospital in Newfoundland will be given a chest x-ray, free of charge. The introduction of such a service answers a long felt need among tuberculosis workers in this province, since the sick and infirm comprise that group yielding the largest percentage of active cases of tuberculosis. This is understandable in view of the fact that tuberculosis is a communicable disease, known to make little or no headway when it attacks a healthy person, but which progresses rapidly in a body whose resistance has been weakened by illness of any kind.

"Hospital admission chest x-rays provide an excellent means of picking up cases whose tuberculosis might be masquerading as some other ailment, the symptoms of which are similar to those of tuberculosis. The programme will also cover persons who might evade the usual methods of detection, such as mass chest x-ray surveys, and pre-employment chest x-rays.

"Apart from its value as a case-finding factor, the programme will serve as a powerful preventive measure by eliminating the possibility of either patients or hospital personnel being exposed to infection from tuberculosis. Hospital admission chest x-rays also assist the doctors in diagnosing their patients' illnesses, since chest conditions other than tuberculosis are often detected this way.

"Because of the vital issues involved, and the far-reaching benefits to be derived from such a programme, it is felt that the extension of free chest x-ray services to all hospital admissions will mark a definite step forward in this Province's anti-tuberculosis campaign, and in public health generally."

SUMMARY

Previous analyses of the tuberculosis rate amongst general hospital admissions are discussed by way of comparison.

The procedure in force at St. Anthony is outlined and some of the difficulties are enumerated. The findings on admission radiographs at St. Anthony are analyzed.

There were 1234 admissions. Of these, 854 admissions were for symptoms unrelated to the chest; 2.7% were diagnosed as active tuberculosis; 0.93% have to date been proven active.

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RÉSUMÉ

Depuis juin 1954 les autorités de l'hôpital de St. Anthony (Terreneuve) se sont efforcées de mettre en vigueur la radiographie pulmonaire obligatoire de tous les malades admis dans cette institution. En dépit de nombreuses difficultés, la grande majorité des malades y passa. Les auteurs de cet article analysent les résultats obtenus dans la première année et signalent que sur un total de 854 cas ne présentant aucun symptôme en rapport avec les voies respiratoires, 56 ou 6.56% furent classifiés à la radiographie comme tuberculose inactive et 23 ou 2.70% comme tuberculose active. De ces 23 malades, 8 furent effectivement démontrés porteurs de B.K.—Les chiffres de comparaisons semblables rapportées antérieurement sont donnés dans le texte.

AN OUTBREAK OF NEPHRITIS AT TREHERNE, MANITOBA

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ACUTE GLOMERULONEPHRITIS usually occurs in sporadic form, but epidemics are reported. These include the epidemic among Indians at Redlake, Minnesota,[22] in the area of Greenock, Scotland,[11] and in Australia.[18] Furthermore, instances of several cases occurring in a family have been reported by Eason in 1924,[8] Kilpatrick in 1945,[16] Ernstene in 1931,[10] and Tudor in 1943.[27] Siegel in 1955[25] reported that in the past few years some 12 outbreaks of nephritis in the U.S.A. had been studied. It is the purpose of this communication to record an outbreak of nephritis in a community of 700 at Treherne, Manitoba.

The Treherne Epidemic

The epidemic started in the L. family who live on a farm to the north of Treherne. There are eight children in the family ranging in age from nine months to 12 years. B.L., aged 12 years, was the first to fall ill. He had a sore throat and a temperature of 104° F., and developed acute glomerulonephritis nine days later. His brother Br.L., aged nine, and his sister I.L., aged four years and eight months, developed the illness ten days after B.L. The youngest member of the family, E.L., aged nine months, was found to have a pleural effusion without abnormal urinary findings.

Six weeks after the beginning of the epidemic another case occurred in a different family. This was a girl, M.S. aged five years and eight months, whose nephritis started 19 days after a prophylactic dose of benzathine penicillin.

A five-year-old cousin of M.S. from Oklahoma was visiting Treherne at the time that M.S. was ill. This child developed hæmaturia after returning to his home.

Bacteriology of the Epidemic

The occurrence of three cases of acute glomerulonephritis in one family indicated the presence of an organism with a marked capacity for producing this disease. Swabs were taken from the throats of the whole of the L. family and the teacher and children at the school attended by B.L. and Br.L. and submitted to the laboratory of the Provincial Health Department. Of the cases reported in this paper only one, (E.L) gave a growth of beta hæmolytic streptococci; the remainder grew pneumococci. Of the swabs taken from 20 contacts, four grew streptococci. It is unfortunate that in no instance was it possible to group these streptococci, owing to technical difficulties.

Two schoolchildren whose throat swabs grew beta hæmolytic streptococci came from a family

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which had recently suffered from sore throats and high fevers; none developed nephritis. They had been drinking unpasteurized milk from a cow with mastitis, and this was the possible source of their infection. B.L. had been visiting this family and had drunk the milk 12 days before his attack of nephritis.

Milk was considered to be the source of spread in the Australian epidemic reported by Manser and Wilson.[18] It was unpasteurized, and the organism was never grown from it. However, when carriers of streptococci (mainly types 12 and 22) were prevented from handling the milk, the outbreak subsided.

THE CAUSATIVE ORGANISM—DISCUSSION

In the past it has been suggested that the pneumococcus may cause nephritis.[4, 12, 28] Claims have also been made for the alpha hæmolytic streptococcus[17] and the typhoid bacillus.[2] In the present series, although the pneumococcus was the sole organism isolated from the cases of nephritis, their antistreptolysin titres were 833 units. In four weeks this fell to 333 units. It was concluded that these children had recently been infected with a streptococcus. If antistreptolysin titres were determined in all cases (if possible in a controlled series), the role of the various organisms mentioned could be made clear.

Rammelkamp[20] has shown that the development of nephritis is related to the serological type of the streptococcus, type 12 producing the highest attack rate. He also states that the antibody to type 12 can be demonstrated in the patient's serum six years after infection.

PROPHYLAXIS AND PREVENTION

The prophylaxis of rheumatic fever by means of sulfonamides or penicillin is well accepted. Evidence is accumulating that epidemics of acute nephritis can be prevented by penicillin in adequate doses. Denny *et al.*[5] showed the preventive value of early penicillin treatment of streptococcal infections. Weinstein[30] showed that if penicillin was used in the treatment of streptococcal infections those cases with sequelæ had no abnormality of sedimentation rate, antistreptolysin and antistreptokinase titres. Chamonitz and associates[3] have reported that a single injection of benzathine penicillin (600,000-1,200,000 units) is more effective in the prevention of rheumatic fever than three doses of procaine penicillin given every other day. Reinstein[22] reported a successful mass prophylaxis of 1997 persons in the Red Lake epidemic of nephritis by the use of benzathine penicillin. The incidence of beta hæmolytic streptococci on throat culture dropped from 20.7% to 1.3%. No further cases of nephritis occurred. It would seem therefore that epidemics of nephritis can be controlled, and that this should be done as a public health measure.

In the Treherne epidemic 1,200,000 units of a mixture of crystalline procaine and benzathine penicillin were administered to all the children in the district, the school teacher and the parents of the L. family and the W. family. Nineteen days after this dose of penicillin was given the last case in the epidemic occurred. This would suggest that the effects of a single injection of long-acting penicillin may not last for a full 30 days as claimed. In Winnipeg one long-acting penicillin has been tested and it was found that effective blood levels were maintained for only 18 days.[6] Moreover, a child known to have nephritis, whose progress was followed in the out-patient department at the Children's Hospital, Winnipeg, was given 1,200,000 units of long-acting penicillin at monthly intervals prophylactically. He had an acute recurrence of nephritis with hæmaturia 29 days after one of the injections. Although these experiences are limited, it would seem wise to give prophylactic doses of long-acting penicillin at more frequent intervals than once a month. Injections every two to three weeks would presumably offer more effective protection.

In order to discover subclinical cases, the urine of the other members of the L. family and the W. family was examined and found to be normal. In several epidemics unsuspected cases have been found by doing Addis counts on urine samples. After examining a large number of controls, Siegel[24] considered the excretion of 10 red blood cells/c.mm. to be the upper limit of normal. People with a variety of infections can show a transient increase in red cells in the urine and this must be considered when such findings are interpreted. The progress of such cases must be followed, and treatment should be instituted for those in whom repeated tests are positive.

If laboratory facilities are not available locally, cell counting on the scale necessary for screening purposes may not be practicable. The authors therefore would like to suggest that the

screening be done by means of a chemical test for hæmoglobin rather than by a microscopical test for red blood cells. A tablet test is available in which *o*-Tolidine turns a blue colour when oxidized by the peroxidase activity of hæmoglobin. Watson-Williams[29] has investigated the application of such a test as a routine measure for the detection of blood in urine. It will show the presence of 50 red blood cells/c.mm. in two minutes, and less than this within four minutes. We repeated part of Watson-Williams's investigation with the "Hæmatest" tablet, and found it satisfactory. This, combined with the use of 3% sulfo-salicylic acid to test for albumin, should make it possible to screen the urine of a large number of people simply and efficiently.

TREATMENT

Bed rest, antibiotics and dietary restrictions are the main lines of treatment in the acute case. It is usual to ensure bed rest until œdema has disappeared and blood pressure and urinary volume have returned to normal. Rubin and his colleagues[26] state that the erythrocyte sedimentation rate is the most reliable guide to the activity of the disease. Urinalysis returns to normal first and is probably the least helpful. They found that the Addis count returned to normal about five weeks after the sedimentation rate fell. Real recovery is when the Addis count and sedimentation rate have remained normal for several consecutive weeks. There would however appear to be little to recommend complete bed rest until this latter state is attained.

Fluid restriction is wise in the early stages until the urinary volume returns to normal. Salt restriction is practised when œdema is present. Subsequent dietary management is a more controversial question and many still believe in limiting first-class protein, and in particular red meats. Illingworth, Philpott and Rendle-Short[14] carried out a carefully controlled study in 42 cases of acute glomerulonephritis. They were unable to demonstrate any advantage in protein restriction.

Penicillin is the antibiotic of choice, and administration should be maintained for at least 7-10 days. Very few cases have been reported in which ACTH or cortisone has been used in treating acute nephritis. Presumably this is due to the fact that, in children at any rate, acute nephritis clears rapidly and carries a good prognosis. Thorn *et al.* (1950) recorded six cases so treated and concluded it had no good effect; indeed in one case œdema, hypertension and azotæmia proved troublesome. They further noted that gross hæmaturia and the sedimentation rate improved rapidly with ACTH but recurred as soon as the drug was withdrawn.

SUMMARY

An epidemic of nephritis in the community of Treherne, Manitoba, is outlined. A quick method of screening urine for blood using "Hæmatest" tablets is described. It is postulated that if injections of long-acting penicillin are to be used prophylactically they should be given more frequently than once a month.

CASE REPORTS

CASE 1. B.L.—This 12-year-old boy was admitted to the Children's Hospital, Winnipeg, on May 24, 1955. There was a history of sore throat and fever for 13 days, and hæmaturia for 4 days. On admission he had slight œdema of the eyelids with clinical evidence of heart enlargement, which was confirmed radiologically. His electrocardiogram showed left ventricular hypertrophy. Sedimentation rate (E.S.R.) was 48 mm. in one hour; blood urea nitrogen (BUN) 64 mg. %. The urine contained 300 mg. % of albumin with 15-20 leukocytes and 25-30 erythrocytes per high power field (uncentrifuged). He was treated with intramuscular penicillin until June 3, 1955, when he developed a swinging temperature and a grade I apical systolic murmur. At this time erythromycin, and subsequently aureomycin, was given. On June 6, when he showed increasing fever and hæmaturia, hydrocortisone 20 mg. every 6 hours was commenced. Two days later he developed measles. It is interesting to note that hæmaturia practically ceased four days after hydrocortisone was commenced. Antistreptolysin titres on June 9 and July 14, 1955, were 833 and 333 Todd units respectively. He showed gradual improvement at home. E.S.R. on August 12 was 16 mm. in one hour. On October 29 his urine contained no albumin and no red blood cells.

CASE 2. Br.L.—An eight-year-old brother was admitted on May 31, 1955. He had a history of sore throat and fever for seven days, with hæmaturia for one day. This boy had classical urinary findings and a sedimentation rate of 47 mm. in one hour. Physical examination was negative. By June 9, 1955, the urine was practically normal. Antistreptolysin titres were identical with those in the first case. His urine was completely clear by September 3, 1955.

CASE 3. I.L.—This 4½-year-old girl gave a similar history to that of her brother B.L. when admitted on May 31, 1955. She was not as ill as Br.L. but, in addition to a raised sedimentation rate, her blood pressure was 126/100 mm. Hg, BUN 72 mg. %,

and she had a transient grade I apical systolic murmur.

Her antistreptolysin titres were identical with those of her brothers. She was discharged from hospital on June 13, 1955, at which time her blood pressure was normal and she had no heart murmur. Her urine still contained 175 mg. % albumin with occasional leukocytes and 3-10 erythrocytes per high power field. A trace of albumin and a few red cells were still present on October 29.

Comment.—This child developed nephritis 19 days after her brother, B.L. She had a sore throat, for which on the fourth day of illness she was given oral penicillin and sulfonamide mixtures. Ten days after this medication was started she showed signs of nephritis.

CASE 4. E.L.—The youngest of this family, aged nine months, was admitted on May 31, 1955, with a red throat, running nose and cough. Urinary findings were negative. A radiograph of chest showed a pleural effusion 1 cm. wide on the right side extending from base to apex. He was the only member of the family in whom a throat swab grew beta hæmolytic streptococci (non-groupable). A second radiograph on June 6, 1955, showed the pleural effusion to be resolving and some linear infiltration in the right middle lobe.

Comment.—This case is of particular interest because it is the only one in which beta hæmolytic streptococci were grown although no signs of nephritis were ever seen. Fleming[11] reported that in 15% of his cases of nephritis pulmonary consolidation occurred.

CASE 5. M.S.—This 5¾-year-old female developed nephritis June 25, 1955. She was never admitted to hospital. She had received 1,200,000 units of a mixture of crystalline, procaine and benzathine penicillin on June 6, 1955. Her initial complaint was of painful micturition.

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RÉSUMÉ

Une petite épidémie de néphrite survint à Treherne (Manitoba) au printemps de 1955. En un mois dans ce village de 700 âmes, trois enfants d'une même famille, un visiteur et un enfant d'une famille avoisinante furent atteints. La source de l'infection aurait été retracée à une vache souffrant de mastite et dont le lait non pasteurisé aurait transmis le microbe néphritigène. Même si le streptocoque β hémolytique ne fut isolé que de la gorge d'un seul malade, tous montrèrent un titre élevé mais décroissant d'antistreptolysine. Les autres enfants de la région ainsi que les adultes exposés au contact des malades reçurent une injection de 1,200,000 u.i. d'un mélange de pénicilline cristalline et benzathine, à titre de mesure préventive; cependant le dernier cas se déclara 19 jours après cette injection. L'Hæmatest (*marque déposée*) fut employé dans le dépistage de l'hématurie.

THE EFFECT OF MYOCARDIAL INFARCTION ON THE SIZE OF THE HEART

Weiss *et al.* (*Am. J. M. Sc.*, 234: 129, 1957) made a roentgenologic follow-up study on 489 patients who survived an acute myocardial infarction for at least two months and who had a normal-sized heart at the time of the infarction. Only patients who had recovered from their presumed first infarction were included. The majority were observed for from one to 10 years.

Two per cent (eight cases) developed cardiac hypertrophy in the absence of generally accepted factors such as hypertension, valvular heart disease or cor pulmonale. Cardiac enlargement was first noted from six months to 13 years after the onset of the infarction. All eight patients who developed cardiac hypertrophy had associated congestive heart failure. Multiple myocardial infarctions did not cause cardiac hypertrophy in the absence of congestive failure. The opinion is expressed that cardiac hypertrophy develops with congestive failure, which in turn results from a myocardial aneurysm or extensive myocardial fibrosis, or both these complications of the myocardial infarction.

SYMPOSIUM ON THE CLINICAL SIGNIFICANCE OF ALDOSTERONE*

I. FACTORS AFFECTING ALDOSTERONE EXCRETION†

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C. J. P. GIROUD, M.D. and
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ALDOSTERONE is the latest addition to the family of biologically active adrenal cortical hormones. Although its existence in the amorphous fraction had been suspected for many years, only in 1953 was it isolated from adrenal extracts by Grundy, Simpson and Tait.[1] In 1954 its chemical structure was established through the collaboration of groups in Switzerland and England.[2]

Aldosterone has aroused considerable interest because for the first time it has been demonstrated that the release of an active hormone from the adrenal cortex can be affected by other factors besides adrenocorticotrophin.

Because of the great difficulty in extracting significant amounts of aldosterone from natural sources and the poor yields obtained at the present time in the synthesis of this hormone, only very small amounts have been available for clinical use and our knowledge of its physiological effects in man is meagre. In the few clinical studies reported, aldosterone affects essentially sodium metabolism.[3-6]

Aldosterone is excreted in human urine, and its measurement in this fluid has yielded information on some of the factors influencing its elaboration in healthy subjects and in patients with various diseases.

The bio-assay used for the analysis of aldosterone in our studies is a modification of the Singer-Venning procedure[7] and is based upon the effect of aldosterone upon sodium excretion in the adrenalectomized rat. The extract obtained after acid hydrolysis of the urine is subjected to a chromatographic fractionation on paper, and the aldosterone fraction is eluted and submitted to bio-assay.

RANGE IN NORMAL INDIVIDUALS

Using this procedure, the range of excretion of aldosterone in healthy males was found to be from 1 to 7 μg. with an average value of 3.5 μg. per 24 hours. In a smaller group of healthy females, the range was from 1.7 to 5.5 μg., the average being 3.8 μg.[7] Fluctuations occurred in the daily excretion of aldosterone in the same person within the range given. In some subjects a diurnal variation in the output of aldosterone was observed but not consistently.

EFFECT OF ACTH AND HYPOPHYSECTOMY

Conflicting reports are found in the literature about the influence of ACTH on aldosterone excretion. Most of the earlier workers failed to show any increase in the output of this hormone following administration of ACTH in man,[8, 11] and Luetscher[12] found normal levels of aldosterone in patients with panhypopituitarism. Studies on hypophysectomized rats by Singer and Stack-Dunne[13] suggested that the anterior lobe may play some role in the regulation of aldosterone release, whereas, in hypophysectomized dogs, Farrell *et al.*[14] found that ACTH had only a slight effect. Recent studies by Liddle *et al.*[15] and by Venning, Dyrenfurth and Beck[16] indicate that ACTH does have some influence on the release of aldosterone. The discrepancy between the findings of the various groups can be attributed in part to the methods used for the preparation of the urinary aldosterone fraction.

In the following study (Fig. 1) 100 mg. of ACTH* was administered i.m. for three days to a healthy male and the levels of aldosterone, corticosteroids, 17-ketosteroids and urinary sodium were followed up for 14 days. Urine collections were begun on a day on which this student had a written examination and the higher output on this day is believed to have been due to anxiety, as similar effects have been observed in other students.[7] On the three days before administration of ACTH the aldosterone excretion ranged between 1.3 and 2.0 μg. per 24 hours. Coincident with the administration of ACTH it increased to 5.6 μg. and remained at that level until 24 hours after withdrawal of ACTH. Following this, the aldosterone decreased to pre-treatment levels. Other studies have shown the same effect.

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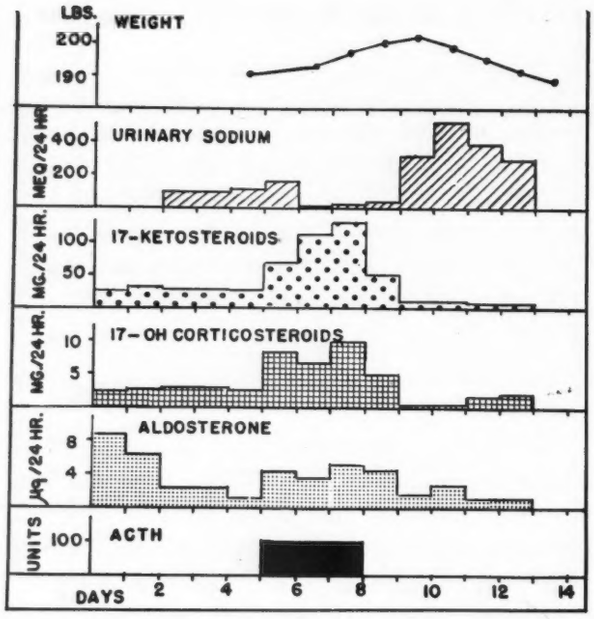

Fig. 1.—Effect of ACTH on aldosterone excretion in a healthy subject.

Prolonged administration of ACTH to patients with rheumatoid arthritis showed that the initial effect of ACTH was to increase aldosterone excretion, as shown in Fig. 2. However, as therapy was continued, aldosterone excretion gradually decreased to barely detectable levels. When therapy stopped a diuresis occurred and the patient showed a marked negative sodium balance. Aldosterone excretion then increased to 12 µg. per 24 hours. With a second administration of ACTH the excretion of aldosterone again showed a temporary increase.

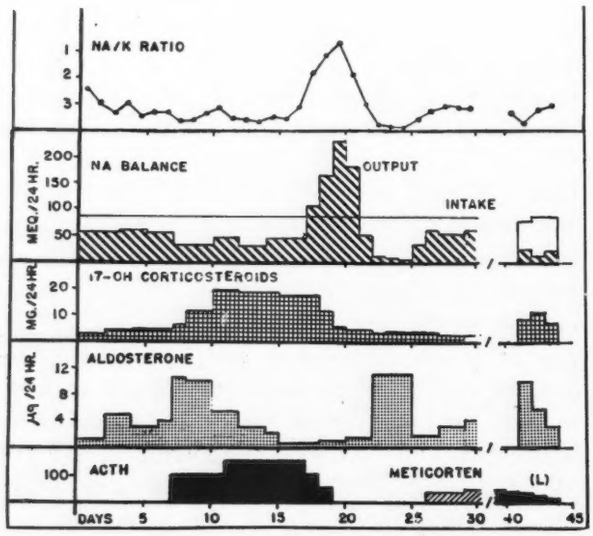

Fig. 2.—Effect of prolonged administration of ACTH on aldosterone excretion in a patient with rheumatoid arthritis.

Although ACTH does appear to have some influence on the release of aldosterone from the adrenal, many patients with hypopituitarism have a normal output of this hormone. In three out of eight patients studied at our clinic who had had hypopituitarism for many years, no demonstrable aldosterone activity in urine could be shown. The other five had low to normal amounts. The administration of ACTH to three of these patients did not result in an increased output of aldosterone. This failure to respond might be due to the fact that the adrenal

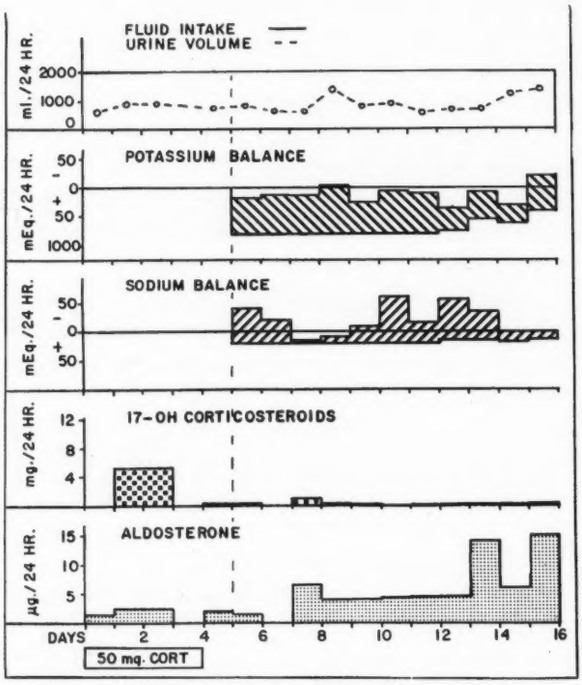

Fig. 3.—Effect of a low sodium intake on aldosterone excretion in a patient with hypopituitarism.

gland was atrophied in these cases. One patient with hypopituitarism did, however, show a significant increase in aldosterone excretion after ACTH administration.

The possibility that there are other trophic factors besides adrenocorticotrophin capable of stimulating aldosterone secretion has been suggested by Rauschkolb and Farrell.[17] These authors have recently obtained evidence that aldosterone secretion is also controlled by a circulating trophic hormone elaborated by the diencephalon.

Effect of Sodium Intake

The original observations of Leutscher and his colleagues[11, 18] showed that sodium intake in-

fluenced aldosterone excretion. Normal subjects placed on a low salt intake of 10 mEq. increased their aldosterone output. Conversely, sodium loading, resulting in sodium excretion of over 500 mEq., was followed by a disappearance of measurable aldosterone from the urine. These findings have been confirmed by other investigators. In the following experiment the effect on aldosterone excretion of reducing the sodium intake from 130 mEq. to 8.7 mEq. per day was studied. A constant intake of fluid was maintained in this healthy subject. The aldosterone ranged from 4 to 6 μg. per day in the control period. On the third day after sodium intake, 200 ml. albumin was administered intravenously. The result of this expansion in blood volume was to cause a decrease in aldosterone excretion in spite of the fact that the subject continued to be maintained on the low sodium intake.

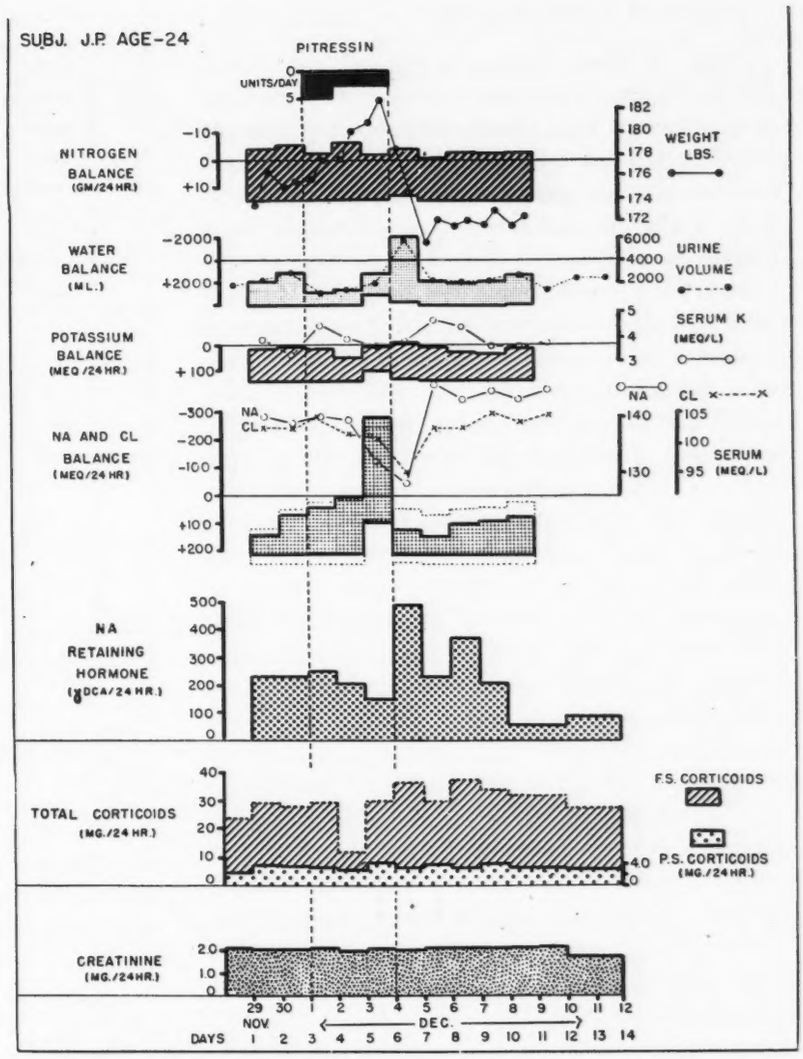

Fig. 4.—Effect of hydration on aldosterone excretion in a healthy subject maintained on a constant sodium intake.

A study on a patient with severe panhypopituitarism showed that a reduction of sodium intake also increased the aldosterone excretion (Fig. 3). Aldosterone assays carried out on various occasions on this patient varied from 0 to 2 μg. per day. After a few days on a diet in which the sodium was restricted to 20 mEq. the aldosterone output increased to 5 μg. On the ninth day the caloric and electrolyte intake was further reduced by the patient's unwillingness to eat and a further increase in aldosterone output to 14 μg. per day was observed. The results obtained in this patient are evidence that the effect of electrolyte intake on aldosterone excretion is not mediated via the pituitary.

Conditions which tend to cause both fluid and sodium loss lead to a rise in aldosterone excretion. Falbriad *et al.*[19] have reported that profuse sweating as well as the administration of acetazoleamide (Diamox) results in increased aldosterone excretion. In a patient with "salt losing nephritis" Luetscher and Curtis[20] have observed an elevated aldosterone output.

Effect of Potassium Intake

Potassium intake may also influence aldosterone excretion. Laragh and Stoerk[21] reported that an excess of potassium in the diet in dogs caused a sevenfold increase in aldosterone. In man Luetscher and Curtis[20] showed that an increased potassium intake was followed by a sodium diuresis associated with a rise in aldosterone output, and in patients with severe potassium depletion a reduction in urinary aldosterone was observed. These findings indicate that the effect of potassium on aldosterone is opposite to that of sodium and may be in some way related to changes in sodium metabolism.

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EFFECT OF FLUID VOLUME

Many of these studies suggested that aldosterone excretion was also influenced by changes in the various fluid compartments. Experiments were carried out by Beck *et al.*[22] in an attempt to elucidate this question. Healthy male subjects were hydrated and were given Pitressin in a manner similar to that described by Leaf *et al.*[23] Under these conditions there occurred a retention of fluid, an increase in urinary sodium and a decrease in serum sodium. If sodium loss was the dominant factor in influencing aldosterone excretion, then under these experimental conditions a rise in aldosterone should occur. Actually the aldosterone decreased slightly during the administration of Pitressin, as seen in Fig. 4, and only on withdrawal of Pitressin did a rise in aldosterone levels occur. These experiments suggest that an expansion of fluids can overcome the stimulus for increased aldosterone excretion caused by a sodium loss. Coincident with the water diuresis following cessation of Pitressin administration, this stimulus became effective and a rise in aldosterone was observed. Liddle *et al.*[24] showed a similar effect with Pitressin in healthy hydrated subjects maintained on a low salt diet. Because of the high initial aldosterone excretion the effect of hydration in suppressing aldosterone was more apparent. Muller *et al.*[25] have confirmed these findings and have also observed a decrease in aldosterone excretion in healthy subjects maintained on low sodium intakes during eight hours of acute water loading without Pitressin.

Bartter *et al*[26] have reported that dehydration without sodium deprivation induces a rise in aldosterone excretion in normal individuals and in patients with hypopituitarism and diabetes insipidus.

We have observed an increase in aldosterone excretion in healthy men maintained on a constant sodium intake following the reduction in fluid intake from 3000 ml. to 250 ml. per day. In Fig. 5 is shown one of these studies. The aldosterone levels began to rise on the third day of dehydration, reaching a peak of 14 μg. per 24 hours. During this period there was sodium retention and an increased potassium excretion. Following hydration the aldosterone levels gradually returned to normal.

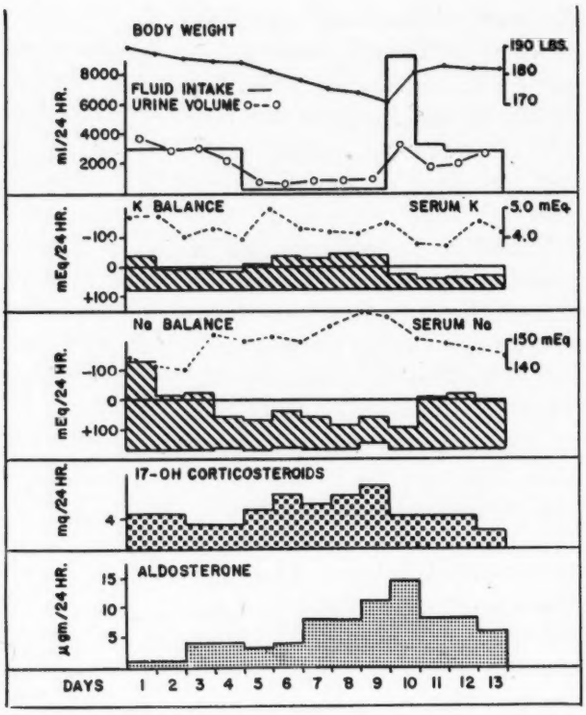

Fig. 5.—Effect of dehydration on aldosterone excretion in a healthy subject maintained on a constant sodium intake.

Thus in both the hydration and dehydration studies, aldosterone excretion was found to be controlled by a function of fluid volume which was independent of sodium changes.

STRESS

We have already mentioned that we have observed a rise in aldosterone excretion in healthy persons during a period of emotional stress such as acute anxiety.[27] In order to investigate this further, the excretion of aldosterone was followed in a series of 18 students under control conditions and during examinations. Not all the students experienced the same degree of anxiety. Those who claimed they were under only mild stress showed little change in aldosterone levels. The students who experienced the greatest degree of emotional disturbance showed an increase in aldosterone levels beyond the normal range. It is extremely difficult to evaluate the degree of emotional stress, but these studies do suggest that in certain individuals acute anxiety may be associated with a rise in aldosterone excretion. Lamson *et al.*[28] reported recently that nonpsychotic subjects with anxiety neurosis showed significantly higher excretion rates of aldosterone than normal subjects.

SUMMARY

Aldosterone elaboration in healthy individuals can be influenced by various factors. An increase in aldosterone excretion is observed after ACTH administration, decreased sodium intake or sodium loss by diuresis or sweating, potassium loading and a reduction in body fluid volume.

A decreased aldosterone excretion can be demonstrated following sodium loading and an expansion of body fluid volume.

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II. EFFECTS OF ALDOSTERONE AND SOME CLINICAL IMPLICATIONS*

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ALDOSTERONE is mainly notable for: (a) its salt retaining potency and (b) its scarcity. The latter factor has undoubtedly delayed any clear or final definition of the actions of this hormone. Our knowledge is extensive but fragmentary and requires confirmation on many points. It is true that at physiological levels the important effects of desoxycorticosterone (DOC) and aldosterone are very similar, but it is not justifiable yet to pronounce them identical, or to infer that aldosterone will exhibit in all respects the well-known actions of DOC. In fact, at levels somewhat above those believed to be physiological significant differences have been demonstrated.

PHYSIOLOGICAL EFFECTS OF ALDOSTERONE

On Electrolytes

The first studies with pure aldosterone were made in 1953. Desaulles[1] reported that aldosterone was about 25 times as potent as DOC in respect to sodium retention and 5 times as potent in respect to potassium excretion. Mattox[2] and Speirs[3] found aldosterone 100-120 times more potent than DOC in altering urinary sodium/potassium ratio, and effective at doses of 0.1 μg. in rats. Subsequent reports have confirmed these findings. In terms of substitution therapy in adrenal insufficiency a figure of about 30 times appears to be more realistic.

It has been shown in several species that administration of aldosterone decreases urinary sodium. This can occur in the presence of an increased glomerular filtration rate and increased filtered sodium load and hence is indicative of increased tubular reabsorption of sodium. There are concomitant changes in urinary excretion of hydrogen and potassium ions. Bartter[4] has suggested a mechanism of action of aldosterone in the kidney. In an attempt to account for known facts, he postulates two sites of sodium reabsorption from the tubules, both influenced by aldosterone. The one more proximal includes NaCl absorption and exchange of H^+ for Na^+ in sodium hydrogen phosphate. The more distal mechanism involves an exchange of Na^+ for K^+ or H^+, the H^+ being accepted if ammonia is available for ammonium ion formation. This second mechanism can lead to hypokalæmic alkalosis.

Direct support for these hypotheses is meagre, but Nicholson[5] has reported recently that aldosterone (at low dose levels at least) exerts its

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main effect in the proximal and not the distal tubule. No effect on potassium excretion was observed. This does not mean that at higher dose levels or under different conditions aldosterone may not act also on the distal mechanism, which may or may not be in the distal tubule.

On Life Maintenance

The life maintaining effect of aldosterone in adrenalectomized animals is a reflection of its salt retaining properties and hence is demonstrable at much lower doses than with DOC.[6, 7] The beneficial effects of commercial adrenal cortical extracts are probably due mainly to their aldosterone content, which is about 5 μg. per ml. The hundredfold higher glucocorticoid content would seem relatively insignificant by comparison.

From Clinical Studies

Mach *et al.*,[8] Thorn *et al.*,[9] Prunty *et al.*,[10] Kekwick and Pawan,[11] Salassa *et al.*,[12] Muller,[13] Griboff *et al.*[14] and Beck *et al.*[15] have observed the effects of aldosterone given by different routes in doses ranging from 100-1000 μg. per day to normal individuals and to Addisonian patients. The hormone appears to be most effective when given in aqueous solution intramuscularly in divided doses. It acts quickly to cause retention of sodium and chloride. With moderate doses in Addisonians, and larger doses in normals, it causes water retention and potassium excretion. At very high levels, or in acute intravenous studies, a fall in eosinophil count, ACTH suppression and other glucocorticoid effects have at times been reported but not always confirmed. There is general agreement that 150-250 μg. per day will provide replacement therapy in Addison's disease.

Further light on the actions of aldosterone is obtained from reports by Conn[16] and others of patients with aldosterone-producing tumours of the adrenal cortex. These effects include the biochemical changes hypokalæmia, hypernatræmia and alkalosis, and the clinical findings of weakness, hypertension and a polyuria unresponsive to Pitressin. The patients were found to be in sodium balance but to have depressed sweat and salivary sodium, increased intracellular sodium and decreased potassium in muscle biopsies.

On Water Balance

Water retention is not commonly observed with aldosterone administration unless the dose is excessive. The effect then may be due to excess salt retention, altered renal hæmodynamics or other factors. On the other hand, the chronic high levels associated with aldosterone producing tumours may be accompanied by polyuria. This could be an anti-Pitressin effect, or secondary to polydipsia induced by salt retention, or quite possibly due to the renal tubular damage. Against the stress of water intoxication aldosterone offers about the same protection as cortisol[17] and hence has no physiological importance. Cases of severe idiopathic œdema associated with sodium retention and high urinary aldosterone have been observed,[18] but it is not yet certain whether this may at times represent an alternative syndrome of primary hyperaldosteronism.

On Acidosis

The work of Sartorius[19] with adrenal cortical extract suggests that aldosterone may be the adrenal hormone necessary for efficient acidification of urine and the sparing of sodium by ammonia production. More studies are needed on this subject. In a young child with idiopathic renal acidosis we[20] were unable to detect any aldosterone in the urine.

In collaboration with Dr. S. Munroe we have confirmed the observation that daily injections of adrenal cortical extract will prevent depancreatized dogs from dying of ketosis. At a time when the CO_2 combining power was around 35 vol. % and the blood ketones 27 mg. %, the extract was replaced by two daily injections of aldosterone, each 20 μg. in aqueous 20% ethanol, for one week. The CO_2 combining power rose slightly and the blood ketones fell by 25% during this period. These data are unpublished pending the availability of sufficient aldosterone to repeat the experiment.

Other Sites of Action

The effects of aldosterone on electrolyte metabolism have been demonstrated not only in the kidney but also in the salivary glands,[8, 21] intestinal mucosa,[22] muscle cells[23] and indirectly in the sweat glands.[16] One can probably assume that the electrolyte equilibrium between almost all body cells and their environment is influenced to some extent by the level of circulating aldo-

sterone. Work with DOC[24], however, indicates that different tissues (aorta, brain, skeletal muscle) may be affected in different ways.

Glucocorticoid Effects

A good deal has been written about the fact that in addition to its salt-retaining potency, aldosterone possesses glucocorticoid properties roughly ¼ as great as cortisol and 1/3 those of cortisone. In protecting animals against the stress of cold,[25] water intoxication[1] or allergic reaction,[26] and in its effects on eosinophils,[3] carbohydrate metabolism[27] and renal plasma flow,[17] aldosterone shows a definite glucocorticoid effect if present in relatively high concentration.

In regard to connective tissue inflammation and granulomas, Desaulles,[28] Romani[29] and Jasmin and Richer[30] have described pro-inflammatory effects of aldosterone. Selye[31] found that cortisol inhibition of granuloma formation could be blocked by aldosterone, but this hormone is no more antagonistic to glucocorticoids than DOC, and levels equal to DOC were required. Ward and Hench[32] could find no evidence of either harmful or beneficial effects in rheumatoid arthritis in doses up to 1 mg. a day.

It must be kept in mind that probably all these effects are observed at hormone levels that rarely if ever will occur clinically. Aldosterone production and excretion is roughly 1/1000 that of cortisol. In its mineralocorticoid effects aldosterone has real significance because it is about 2000 times as potent as cortisol. In its glucocorticoid effects aldosterone probably has no physiological significance whatsoever.

Miscellaneous Effects

Meier and Bein[33] have reported that aldosterone maintains the blood vessel response to adrenaline and histamine in adrenalectomized cats. This is a unique effect on the peripheral vasculature and was not seen with other steroid hormones.

Reports that aldosterone will maintain lactation following adrenalectomy,[34] will restore the response to growth hormone following adrenalectomy[35] and opposes the chronaximetric effects of cortisol[36] have appeared. There are reports also of effects of aldosterone on enzyme systems, on kidney alkaline phosphatase[37] and on tissue succinic dehydrogenase.[38] Most of these are probably glucocorticoid effects and may or may not have important physiological importance.

PATHOLOGICAL EFFECTS OF ALDOSTERONE

Because of Selye's hypothesis concerning the etiology of certain "diseases of adaptation" there is great interest in the possible pathological effects of the natural mineralocorticoid aldosterone. We have already considered the effects of aldosterone-producing tumours. Although DOC is known to induce hypertension. Gross[39] could demonstrate no hypertensive effects with relatively large doses, 40μg. per day, of aldosterone administered to rats over a period of 29 days.

In our laboratories Kumar *et al.*[40] demonstrated for the first time in 1955 that long-continued administration of doses of aldosterone closer to physiological levels can produce hypertension in either intact or adrenalectomized rats. The hormone in aqueous 20% ethanol was injected subcutaneously into young rats in doses of 0.5-1.0 μg. every 24-48 hours. After 6-12 weeks a rise in systolic pressure was noted which in 5 or 6 months reached a maximum averaging 75 mm. above control values. The effect was greater than that observed with 50-100 times as much DOC.

In post-mortem studies[41] heart weights per 100 g. body weight of the aldosterone treated rats were 30-40% above control values after eight months. Kidney weights were also increased by 20-50% in this group. Among the hypertensive animals only 4 out of 21 (19%) showed proteinuria and only in this small group were there significant renal changes. In these kidneys a good many glomeruli showed proliferation of the epithelial cells of Bowman's capsule with some thickening of the basement membrane. Our observations serve to emphasize the possible importance of aldosterone in the etiology of idiopathic hypertension, and the pathological changes are not at variance with the renal biopsy studies of Castleman and Smithwick[42] in such patients. We have ventured to suggest that our animals may represent the experimental counterpart of human essential hypertension.

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III. CLINICAL STATES ASSOCIATED WITH ABNORMAL ALDOSTERONE EXCRETION*

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A REVIEW of the many publications dealing with clinical states associated with abnormal aldosterone excretion reveals many contradictory and confusing results. One reason may be due, as was just pointed out by Dr. Venning, to the differences in extraction-hydrolysis procedures. Another, and we believe more important, reason comes from the fact that biological assay of urinary aldosterone, as carried out in too many instances, is unspecific and inaccurate.[1, 2]

Since there are at the present time no specific chemical or physico-chemical methods for the determination of aldosterone in a mixture of steroids or in a urinary extract, the best procedure is to achieve its complete separation from other substances present in urinary extracts. Such a procedure has recently been elaborated in our department and reported at the last International Congress for Clinical Chemistry in New York. It is briefly outlined in Figs. 1 and 2. The results which will be reported from our laboratory have been obtained by this new chemical method.[3, 4a, 4b, 4c]

*From the Clinical Research Department, Hôtel-Dieu Hospital.

The clinical states associated with low or high urinary aldosterone excretion are summarized in Table I.

TABLE I.—CLINICAL STATES ASSOCIATED WITH AN ABNORMAL ALDOSTERONE EXCRETION

A. HYPOALDOSTERONISM.
- Adrenal insufficiency (Addison's disease)
- Following total bilateral adrenalectomy.

B. HYPERALDOSTERONISM.
1. Dietary imbalance
   - Abnormally low sodium intake
   - Abnormally high potassium intake
   - Loss of sodium by excessive perspiration
2. "Stresses"
   - Mental or emotional
   - Anxiety state
   - Surgical operation
3. Pregnancy
4. Pathological states associated with generalized œdema:
   - (a) nephrotic state
   - (b) congestive heart failure
   - (c) cirrhosis of the liver
   - (d) hypoproteinæmia
   - (e) "idiopathic œdema with sodium retention and hyperaldosteronuria".
5. Pathological states associated with increased blood pressure:
   - (a) primary aldosteronism (Conn's syndrome)
   - (b) essential and malignant hypertension
   - (c) toxæmia of pregnancy
   - (d) Cushing's syndrome (mixed form)
6. Familial periodic paralysis
7. Salt-losing form of virilizing adrenal hyperplasia
8. Sodium-losing nephritis.

A—HYPOALDOSTERONISM

Luetscher and Axelrad could not detect any aldosterone by their biological assay method in patients with Addison's disease or in bilaterally

adrenalectomized patients.[5] On the other hand, Girerd and Green have reported an average excretion of 480 micrograms of desoxycorticosterone equivalent in crude urinary extracts from three hypertensive patients totally adrenalectomized and maintained on 125 mg. of cortisone daily.[6]

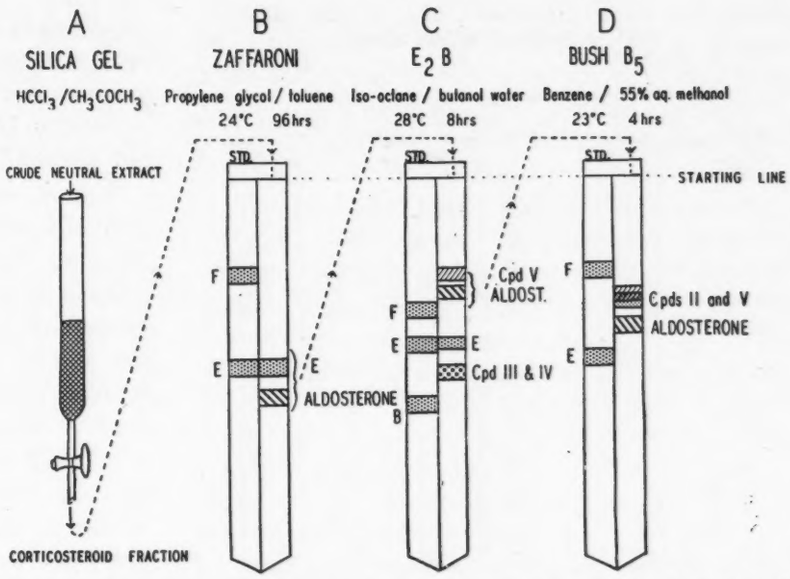

Fig. 1.—Purification of urinary crude neutral extract for isolation of aldosterone. The crude neutral extract of urine is obtained after continuous extraction of urine at pH 1 for 30 hours. Aldosterone contained in this extract is purified as indicated. The Eberlein-Bongiovanni's E_2B system of isooctane/tertiary butanol and water is essential to separate aldosterone from other substances, especially Compound III which has a mobility similar to aldosterone in many other chromatographic systems studied.

B—HYPERALDOSTERONISM

1. Luetscher and his collaborators were the first to show that diets containing only 11 milliequivalents of sodium per day resulted in a four- to five-fold increase in urinary aldosterone.[7-9] This finding was later confirmed by other workers.[10] Muller and Falbriard have demonstrated a greater aldosterone excretion after profuse sweating or severe physical exercise accompanied by perspiration.[11] A similar observation was reported by Streeten and his co-workers.[12]

Excessive potassium intake or an increase in serum potassium, as first noted by Laragh and Stoerk,[13] is followed by an increase in urinary aldosterone. This finding was later confirmed by Luetscher,[8] by Liddle and his co-workers[10] and by ourselves.

We have studied several subjects on high potassium intake (180 to 270 mEq. per day in addition to the basal diet). The response of one such subject with early benign essential hypertension is illustrated in Fig. 3, and the ultraviolet photographs of the chromatograms in the Eberlein-Bongiovanni iso-octane/tertiary butanol and water system are shown in Fig. 4.

2. Mental and emotional stress is often accompanied by an increase in urinary aldosterone output. This was reported by Venning and her collaborators in subjects undergoing the stress of presenting a paper at a scientific meeting or sitting for a written examination.[14] Lamson and his co-workers have reported a uniform increase of urinary aldosterone of 8 to 12.2 μg. per day (normal controls: 2 to 3.3) in each

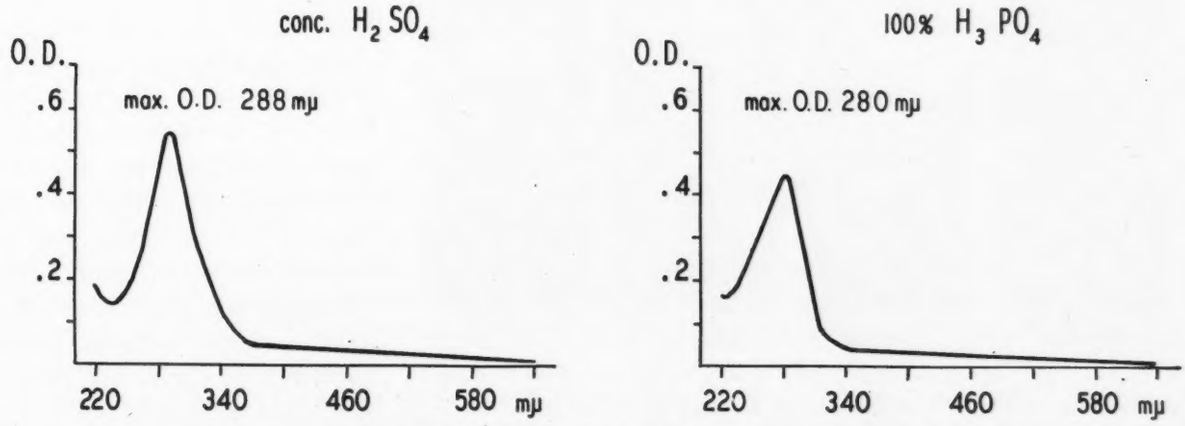

Fig. 2.—Determination and identification of urinary aldosterone. (1) Ultraviolet absorption spectrum of aldosterone fraction. (2) Determination by blue tetrazolium reaction. (3) Identification by absorption spectrum in concentrated H_2SO_4 and in 100% H_3PO_4.

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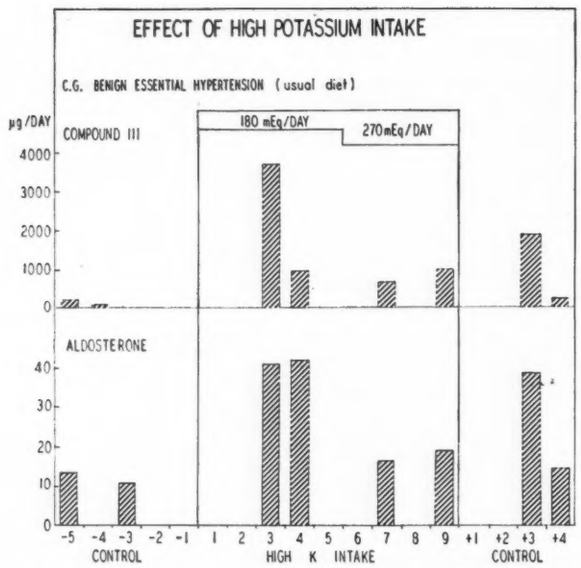

Fig. 3.—Effect of high potassium intake. This patient was a 17-year-old subject with early benign essential hypertension. For nine days the patient received a supplement of 180 to 270 milliequivalents of potassium per day (Potassium Triplex, Lilly). The immediate response to the marked increase in dietary potassium was a fourfold increase in aldosterone excretion and a 100-fold increase in a compound recently isolated and called Compound III. This substance is frequently found in varying amounts in urine hydrolysis with β-glucuronidase and is most difficult to separate from aldosterone in various paper chromatographic systems.

of nine patients with anxiety neurosis.[15] We can confirm these results in five out of six patients with anxiety state (Fig. 5). In none of the patients we studied were there any abnormal physical findings.

Llaurado has been able to extract aldosterone from a large amount of pooled urine passed by patients just recently operated on. The average amount in the postoperative state is about twice the normal.[16, 17]

3. Two reports on aldosterone excretion in normal pregnancy have recently appeared. Venning and Dyrenfurth, using a bioassay method of measurement of the aldosterone obtained after one chromatographic purification of the crude urinary extract, have reported a marked increase in the last trimester of pregnancy.[18] The average excretion of aldosterone was found to be 25 µg. per day, with a range from 12 to 30.

Martin and Mills have studied 55 normal pregnant women.[19] By the method of Neher and Wettstein, the mean excretion at 28 weeks and more was 3.6 ± 2.5 micrograms per day, as compared with an upper limit of 2 micrograms per day in normal controls. Using our new method for the determination of aldosterone, we have studied several normal pregnant women in whom blood pressure was normal and who were free from any œdema or albuminuria.[3, 4, 20] Aldosterone was also determined in a pool of 268 litres of urine from normal pregnant women in their 7th to 9th month of pregnancy.* Results are shown in Table II. The excellent agreement is almost

TABLE II.—URINARY ALDOSTERONE IN PREGNANCY

		Micrograms/day	
		U.V. det'n	*BT det'n*
E.G.	1st - 9th month.....	105	103
"	2nd - 9th "	108	106
B.N.	1st - 6th "	48	45
"	1st - 9th "	69	69
"	2nd - 7th "	57	57
"	2nd - 8th "	172	200
B.V.	2nd - 9th "	59	67
J.M.P.	1st - 9th "	21	17
G.L.	2nd - 8th "	63	66
J.B.	1st - 8th "	102	100
Pooled 268 litres—			
7th - 9th month.....		57	56

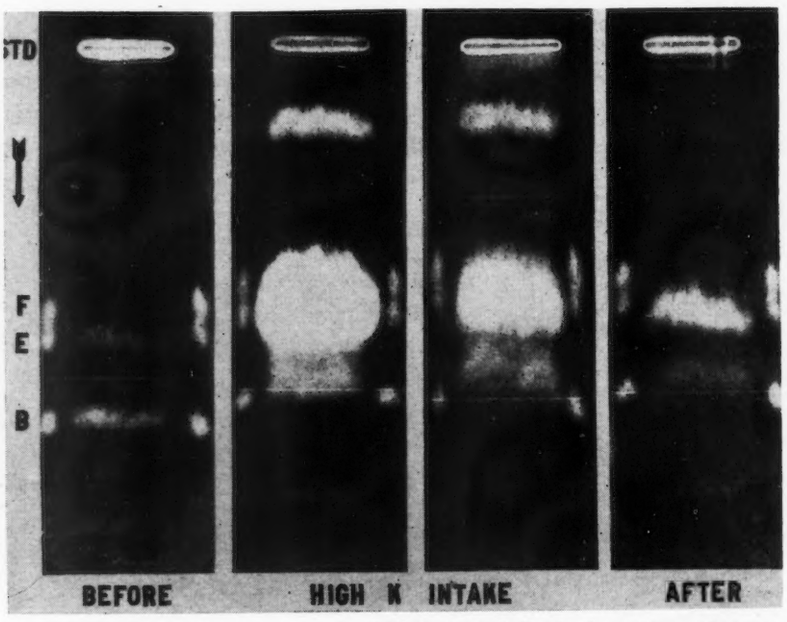

Fig. 4.—Aldosterone zone from Zaffaroni and Bush C systems chromatographed in Eberlein-Bongiovanni's E_2B system. These ultraviolet photographs of the Eberlein-Bongiovanni's E_2B chromatograms are those of the patient described in Fig. 3. They are related to days —3, 3, 4 and +4 of the experiment. The very high amounts of Compound III at the level of the cortisone (E) and the hydrocortisone (F) zone are clearly shown during the period of high potassium intake. Just above this zone can be seen a faint line representing the aldosterone.

*We wish to thank Dr. Gilles Papineau-Couture and Ayerst, McKenna & Harrison Limited, Montreal, for their collaboration.

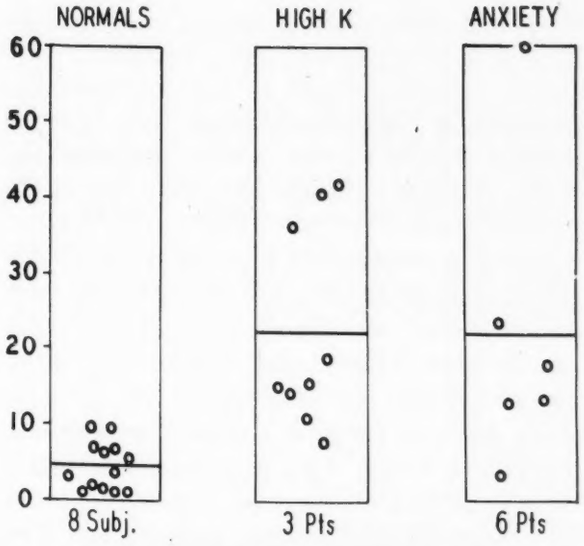

Fig. 5.—Urinary aldosterone excretion (μg./day). Thirteen determinations of urinary aldosterone were done in eight normal subjects with a range of 1.8 to 9.8 μg. per day Three different determinations were done on each of three patients while on a high potassium intake. In the patients with anxiety state and without any other abnormal findings, it is obvious that quite high aldosterone levels can be found.

all cases between the values obtained by ultraviolet determination or by blue tetrazolium reaction and the identification of aldosterone by the spectra in both concentrated sulfuric acid and in 100% phosphoric acid gives great weight to the validity of these higher results.

4. Deming and Luetscher, who were the pioneers in this field, demonstrated in 1950 a significant amount of sodium-retaining factor in lipid extracts of urine obtained from patients with the nephrotic syndrome.[21] In a brilliant series of observations, Luetscher and his collaborators showed that this increase of sodium-retaining activity was due to an increase in aldosterone excretion.[22] In fact, crystalline aldosterone was obtained from urine of such patients and identified by infra-red spectroscopy.[23, 24] After diuresis with cortisone, ACTH or salt poor concentrated albumin, the nephrotic patients show a decrease in urinary aldosterone excretion.[25] These studies have been confirmed by other workers.[26] Similar increases in aldosterone excretion have been found in most cases of congestive heart failure and in almost all cases of cirrhosis of the liver with accumulating ascites by Luetscher, Chart, Singer, Pechet, Bongiovanni, Muller and their co-workers.[22, 27-32] It is interesting to point out here that this increase in urinary aldosterone occurs in spite of the greatly increased body fluid volumes, especially extracellular. This constitutes an important objection to the claim that a reduction in extracellular fluid volume is a major stimulus to aldosterone excretion.[33] In these cases of generalized œdema where aldosterone excretion has been found to be high, there has been a uniformly low urinary sodium excretion.

Increased aldosterone has also been found in patients with severe hypoproteinæmia and œdema.[34] Mach and his co-workers have reported on a 46-year-old woman who had developed generalized œdema since the age of 20 every time the salt intake was above 4 g. per day. The œdema disappeared with a lower salt intake.[35] These authors have studied this patient thoroughly and found that periods of œdema were always accompanied by a higher urinary aldosterone output.

Conn described in 1954 a new syndrome characterized by episodes of severe weakness or paralysis, polyuria, polydipsia, arterial hypertension, lack of œdema, and paræsthesiæ associated with a low serum potassium, a high serum sodium, alkalosis and alkaline urine of low specific gravity.[36, 37] Conn demonstrated the presence of a cortical adenoma, the removal of which resulted in a complete cure of the patient's complaints and biochemical changes. Since then, 43 further cases have been observed and these additional studies have confirmed Conn's original observation.

It is interesting to note here that in some of the cases studied, like the one of Chalmers,[38] aldosterone excretion can be within normal limits or only slightly increased. In two cases in which we had the privilege of studying aldosterone excretion, the latter was about twice the normal. It is possible that these adenomas, like phæochromocytomas, may go through periods of quiescence and of excessive activity.

One patient with a very severe Cushing's syndrome associated with marked electrolyte changes and arterial hypertension showed very high amounts of urinary aldosterone (Table III); urinary levels of 31, 51, 99 and even 210 μg. per day were found. In one other case of Cushing's syndrome not associated with any serum electrolyte disturbances or elevation of blood pressure, the amounts of aldosterone in the urine were within normal limits.

Genest and his collaborators, using a bioassay procedure on a statistical basis, reported in 1955 a significant average increase in urinary aldosterone in patients with severe essential

TABLE III.—CUSHING'S SYNDROME.
B.F., 28-YEAR-OLD MALE.
BILATERAL HYPERPLASIA OF ADRENAL CORTEX

Signs:
B.P. 190/125
Serum Na 153 m.Eq./l.
Serum K 2.45 m.Eq./l.
Insulin-resistant diabetes
Eosinopenia 1, 5, 16, 22/mm.[3]
Purple striæ ++++
Muscular atrophy ++++
Osteoporosis ++++ Spontaneous fractures 7
Tendency to infections
Impotence
Increased body hair growth
17 ketosteroids: 30, 16, 14 mg./day

hypertension or with malignant hypertension.[39] These patients had no salt restriction and did not present any œdema.

Similar findings were reported by Gornall and his co-workers.[40] These findings of a mean increase in urinary aldosterone have been reconfirmed in our laboratory with our new method of determination. One-quarter to one-third of the patients studied excreted aldosterone within normal limits. It is of interest to point out that most patients with renal hypertension studied, and in whom it was possible to demonstrate clearly the presence of renal disease preceding the arterial hypertension, had an aldosterone excretion below the normal average (Fig. 6).

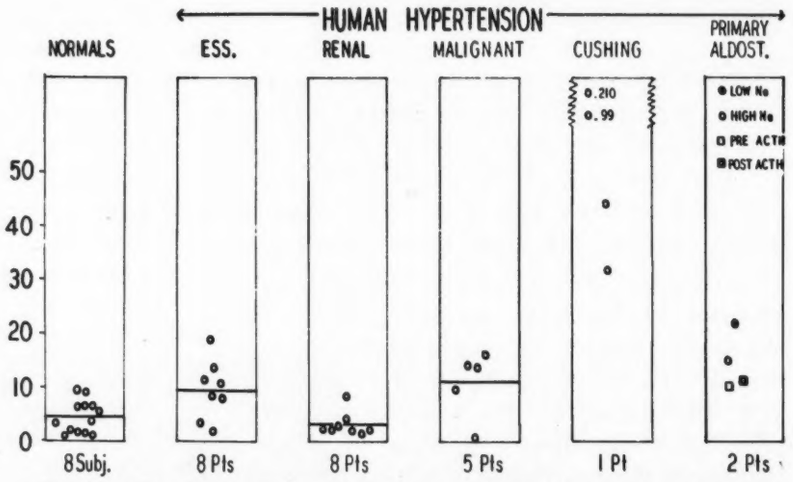

Fig. 6.—This figure shows the urinary aldosterone excretion (μg./day) in various types of human arterial hypertension. The circles represent individual data and the horizontal bars represent the mean of the groups. Two of the 8 patients (Col. 3) with low aldosterone excretion were in the malignant phase of hypertension (with papillœdema and hæmaturia) secondary to chronic glomerulo-nephritis (autopsy findings).

Chart, Shipley and Gordon reported in 1951 an increase in sodium-retaining activity in urine extracts from pregnant women with toxæmia.[41] This finding was confirmed in 1954 by Venning, Singer and Simpson.[42] Recently Venning and Dyrenfurth[18] have re-studied this problem and found a marked increase of total (free and conjugated) urinary aldosterone similar to that found in normal pregnancy. But the free aldosterone fraction was greater in toxæmia. On the other hand, Martin and Mills have recently reported in the *British Medical Journal* an average value of 2.5 ± 2.4 μg. per day in 22 cases of toxæmia.[19] It is difficult to understand the low values found by these authors both in their normal subjects and in their pregnant women and cases of toxæmia.

6. Conn has recently made another very interesting contribution. He established very clearly that the attacks of transient muscular paralysis in patients suffering from familial periodic paralysis were always preceded by marked sodium retention. This was found to coincide with an increase in urinary aldosterone.[43]

7. Prader has reported at the International Congress of Pædiatrics in Copenhagen in 1956, values of 4, 1 and 15 μg. of aldosterone per day in three babies aged one month, three months and one year respectively with the salt-losing form of congenital adrenal hyperplasia. Since these babies were on a high salt intake, the latter two figures were interpreted as elevated.[44] We had occasion to study two such cases. A 2.3 litre aliquot of urine from an infant with this disease contained only 2.7 μg. The second infant excreted 3 μg. of aldosterone per day.

8. Finally, Luetscher found an increase in urinary aldosterone in one patient with a sodium-losing nephritis.[45]

SUMMARY

In summary, we have reviewed the various clinical states associated with high or low urinary excretion of aldosterone and have presented some results obtained in our laboratory with a new method of determination.

It is a pleasure to acknowledge the help of my collaborators, Drs. Barna Vityé, Erich Koiw, Wojchiech

Nowaczynski, Thomas Sandor; of Miss Fernande Salvail, R.N., and Miss Renée Dansereau, R.N., for invaluable help, and of Robert Tellier, Isabelle Morin, Pauline Robinson and Alice Laflamme for their technical assistance.

We are very grateful to Dr. Arnold Relman for the urine specimens from one of the two cases of Conn's syndrome studied by us (results shown in Fig. 6), and to Dr. Claude Migeon, Dr. Lawson Wilkins and Dr. André Davignon for the urine specimens from the patients with the salt-losing form of congenital adrenal hyperplasia.

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IV. PANEL DISCUSSION

Dr. John D. Morrow (Toronto): I would like to report some preliminary observations based on work at Sunnybrook Hospital, carried out in conjunction with Dr. Allan G. Gornall, Dr. H. Fields and Dr. James A. Dauphinee.

Our purpose was to examine the urinary excretion of aldosterone by hypertensive patients. We were particularly interested to observe the effect of varying levels of dietary salt on the excretion of aldosterone in subjects with essential hypertension and to compare this response with that of normal subjects. For this purpose, the subjects were put in a metabolic unit and a constant low salt diet was provided. To simulate normal salt intake, a salt solution containing 7 grams was added daily to the salt poor diet. To produce salt deprivation, diet was administered without supplement. The dietary periods used were eight days, and during the last four days pooled collections of urine were made for aldosterone determination. This determination, a physical-chemical procedure, was carried out in Dr. Gornall's laboratory.

Five hypertensive patients and one normal man were studied. Aldosterone was measured in each of these patients during periods of normal salt intake and salt deprivation. Experience in our laboratory indicates that normal subjects on usual salt intake have a urinary output of aldosterone which is less than 5 μg. per day. Luetscher, Venning and others have reported that this urinary excretion of aldosterone rises when salt is restricted. In a normal subject in this study, both these observations were confirmed.

Two of the hypertensive patients studied showed a significant elevation of aldosterone excretion while on a normal salt intake, the values being 9 and 10 μg. a day respectively. The other three patients all had aldosterone excretion below 5 μg. a day on a usual salt intake. In three of the hypertensive patients aldosterone excretion rose with salt deprivation. One of these had an unusually high level on normal salt intake, the other two did not. In two hypertensive subjects there was no significant increase in urinary output of aldosterone on salt deprivation. One of these had a normal output in the higher salt period.

Two patients were given supplementary potassium sufficient to double their potassium intake in the diet without change in aldosterone excretion.

From this early work, we may conclude that the urinary excretion of aldosterone by hypertensive patients may be normal or may differ from normal in two ways: (1) there may be an unusually high excretion of aldosterone during normal salt intake; (2) aldosterone excretion may fail to rise when salt intake is severely restricted. These few observations suggest that the relationship of aldosterone to essential hypertension is complex and inconstant. We were not able to see any correlation between the severity of the hypertension, its duration, the age of the subject, and the urinary output of aldosterone.

Chairman: Has anyone on the panel any comments to make on this?

Dr. Gornall: I would just like to point out that while hypertensive patients may at times show what appears to be a normal excretion of aldosterone, this does not exclude the possibility that these patients are "hyper-responders" to various stimuli that tend to increase aldosterone production. They do not overrespond to salt restriction, but the problem has still to be worked out.

Dr. Giroud (Montreal): I would like to present briefly the results of some studies which may shed some light on the site of aldosterone production within the adrenal glands.[1] Rat adrenal glands were incubated according to the technique of Dr. Saffran.[2] The adrenals were freed of peripheral fat. A small cut was made in the capsule and the gland was then extruded by gentle pressure. The capsules and the decapsulated glands were incubated separately at 37°C. in Krebs-Ringer bicarbonate solution with added glucose. The incubation media were extracted with chloroform and purified by chromatography and aldosterone was bioassayed according to the method of Singer and Venning.

It was found that what we thought to be the capsule contained not only the connective tissue of the capsule per se, but practically the whole zona glomerulosa and about 1/5 of the zona fasciculata.

A comparison of aldosterone production by rat adrenal "capsules" with that of the corresponding decapsulated glands shows that the "capsules" produced 1.79 ± 0.28 μg. of aldosterone per 100 mg. of tissue per hour, whereas the decapsulated glands produced only 0.14 ± 0.05 μg. of aldosterone per 100 mg. of tissue per hour of incubation. We believe that the data show that, at least in the rat, aldosterone is mainly, if not entirely, produced by the zona glomerulosa. Dr. Ayres and collaborators[3] have obtained similar findings by incubating beef adrenal glands.

Dr. Gornall: Dr. Skelton has reported the very interesting finding that rats develop hypertension and necrotizing vascular disease during regeneration of adrenal cortical tissue after surgical enucleation of these glands. It could be presumed that for a time, at least, the output of aldosterone would be abnormally high. In order to throw some light on this problem we have prepared what we call "pseudo Skelton" rats. Instead of leaving the capsule, we have taken out both adrenals and substituted daily injections of aldosterone. These animals also became hypertensive.

Chairman: I have received a statement that in Toronto two patients, probably with aldosterone secreting tumour, had marked potassium losing diarrhœa. Would the panel care to comment on this? This question is from Dr. K. J. R. Wightman. I wonder if he would care to comment further on these cases?

Dr. Wightman: This is perhaps more relevant to primary aldosteronism. We had two patients whose presenting disorder was a very intense diarrhœa with marked depletion of potassium which was extremely difficult to replace. In one of these cases with Dr. Dauphinee's help, studies of the amount of potassium excreted in the stool were possible, and it was shown to be astronomical. In the other patient it was not possible to carry out detailed observations. One of these patients had an adrenal tumour at autopsy which we failed to preserve for any chemical assay. The other had a tumour in the tail of the pancreas which is probably also of the same histological nature. The question is . . . does this diarrhœa which I mistook for steatorrhœa, and the potassium losing ability of patients with sprue, perhaps indicate another symptom which patients with hyperaldosteronism may exhibit?

Dr. Genest: The patients with primary aldosteronism I am aware of do not usually have diarrhœa. In the cases which you describe, it appears quite difficult to determine whether or not this diarrhœa with marked depletion of potassium may be related to an adrenal tumour of the aldosteroma type. In such cases after elimination of any allergic or local causes, urinary aldosterone should be determined repeatedly, and the adrenals explored surgically if considered necessary.

Dr. Laidlaw: In view of our inability to measure, by any of the methods described, more than a small proportion of secreted aldosterone, would any of the members of the panel care to comment on the nature of the metabolites of aldosterone, with particular reference to the possibility that increased levels of aldosterone in the urine may in some cases indicate not increased secretion but diminished catabolism to biologically inactive products.

Dr. Gornall: I think the first statement we should make is that we know practically nothing about the metabolites of aldosterone. We have some indirect evidence on the question of increased secretion versus decreased catabolism from studies of a patient with cirrhosis, where you would expect to find elevations of aldosterone associated with impaired metabolism. The levels were not much above normal except when there was ascites, so it seems unlikely that we are being misled to any serious extent by instances of decreased catabolism.

Dr. Venning: I would like to agree with Dr. Gornall's statement that we know very little about metabolism of aldosterone.

Dr. Dauphinee: Dr. Venning and others on the panel have shown that one of the things which control the excretion, and presumably therefore the

production, of aldosterone is the volume of extracellular fluid; and they have pointed out that, experimentally, those manipulations which increase the volume of the circulating blood, such as the intravenous administration of plasma albumin, will decrease aldosterone excretion and those conditions which decrease the volume of the circulating blood will increase aldosterone excretion. They have also however called attention to the apparent clinical paradox that in cases of myocardial failure and in patients with cirrhosis of the liver and ascites aldosterone excretion often rises in spite of the fact that in many of these cases there is a simultaneous increase in total blood volume. I would like to suggest that it is not the volume of the whole of the circulating blood which influences the excretion of aldosterone, but rather the volume of blood actually in the arterial side of the vascular tree, or in some particular part of the arterial tree. As far as I know, there is as yet no method for measuring the arterial blood volume separately from the total blood volume but I would venture to predict that in patients who have myocardial failure or cirrhosis with ascites, the volume of blood in the arterial side of the circulation is sharply decreased even though the total blood volume, including as it does the blood on the congested venous side, may be considerably elevated; if this is true, it could explain the paradox mentioned. I would like to ask Dr. Venning what she would say to the suggestion that it is the arterial blood volume and not the total blood volume that is responsible for influencing the output of aldosterone?

Dr. Venning: As Dr. Dauphinee suggests, it may be the arterial blood volume which influences aldosterone excretion. In a recent article, Mach and coauthors comment upon the discrepancies between the findings in normal subjects and in patients with a high aldosterone output associated with an expansion of extra-cellular fluid volume. They suggest that in patients with cardiac failure and nephrosis there may be a diminution of effective circulating fluid which is responsible for the increase in aldosterone excretion.

Dr. Rapoport (Toronto; now at the University of Michigan): I would like to comment on the site of origin of aldosterone in the adrenals. The observations regarding hyperplasia of the zona glomerulosa mostly have to do with animal experiments, especially with rats. However, there is a strong suggestion of species difference as far as the human is concerned. You may recall that in Dr. Conn's patient with primary aldosteronism (*Ann. Int. Med.*, 44: 1, 1956) the uninvolved adrenal showed atrophy of the zona fasciculata. There have been other reports of fasciculata involvement in humans with primary aldosteronism (*Lancet*, 2: 335, 1956). I would also like to ask the panel to comment on the possibility of a central nervous system stimulus to aldosterone secretion.

Dr. Giroud (Montreal): I'm afraid I can't answer the question, except in part. I think that the demonstration, if one can take it for a definite one, that the zona glomerulosa produces aldosterone is not only true for the rat but also, as I pointed out, has been made by Dr. Ayres and collaborators in beef adrenals, and I heard, although I didn't read the paper, that similar findings were obtained quite recently for the dog. It is obvious that from these experiments alone one will not be able to say anything as far as man is concerned, until one incubates human adrenal glands, perhaps by similar methods. I believe that would be quite possible.

Dr. Venning: Recent findings of Dr. Farrell suggest that there is a trophic hormone in the diencephalon which influences aldosterone excretion.

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Case Reports

CONSTITUTIONAL HEPATIC DYSFUNCTION

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CONSTITUTIONAL hepatic dysfunction was first described by Gilbert and Lereboullet[6] in 1902. They called attention to a group of patients in whose blood bile pigments existed in concentrations above normal, whose skin and scleræ were icteric and in whom there were no other physical or laboratory abnormalities. Although the disorder was infrequently mentioned in the next 30 years there have been several reports more recently, among which were those of Rozendaal, Comfort and Snell[9] and of Comfort,[2] Meulengracht[7] and Alwall.[1]

The essential finding in this condition is an increased serum bilirubin of the indirect type. The only striking clinical feature is mild jaundice. The abnormality has also been called

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"intermittent jaundice of the young," "familial non-hæmolytic jaundice," "simple familial cholæmia" and "non-hæmolytic, pre-hepatic jaundice."

The disorder appears to be caused by an inability of the liver to excrete bilirubin in normal amounts. The icterus may be first noted at any age and may be constant or intermittent. It may be familial but does not produce symptoms or affect the health of the individual. In some cases the elevated bilirubin level is discovered accidentally in routine blood tests and may range up to 10 mg. per 100 c.c. The bilirubin is generally of the indirect type but occasionally some direct reacting bilirubin has been reported.

Enlargement of the liver has been noted by some authors studying this condition.[5, 8, 10] Splenomegaly has been reported in a few cases.[3, 4, 11] It should be emphasized, however, that the physical examination is usually completely negative except for icterus. When the spleen is palpable every effort must be made to rule out other causes of splenomegaly and, in particular, the various types of hæmolytic jaundice. In this condition there is no anæmia, no increased reticulocyte count and no evidence of increased normoblastic activity in the bone marrow. The liver function tests are normal except for a decrease in bilirubin in the bilirubin excretion test. The bromsulphalein test should show no excessive retention. There should be no increase in urinary urobilinogen nor should the urine contain bile.

CASE 1.—On a routine examination of aviation cadets, a 21-year-old college student was found to have jaundice. With the exception of migrane he had always been healthy. The family history was negative for jaundice. When seen in November 1952, he complained only of headaches. A physical examination revealed icteric scleræ; the liver edge was felt on deep inspiration but this was not thought to represent hepatomegaly. The laboratory findings are shown in Table I. A roentgenographic examination of the chest and abdomen was normal. Some two years after his jaundice had been discovered the patient continued to be slightly icteric and remained asymptomatic.

TABLE I.—LABORATORY AND ROENTGENOGRAPHIC STUDIES OF 3 CASES OF CONSTITUTIONAL HEPATIC DYSFUNCTION

	Case 1	*Case 2*			*Case 3*
		1943	*1944*	*1946*	
Red cell count, million	5.4	—	—	4.9	5.6
Hb., g. per 100 c.c.	15.3	13.2	13.4	13.0	16.0
Reticulocyte count, per cent	0.6	1.6	1.7	1.8	1.0
Fragility of red blood cells	.44→.30		.46→.26		.48→.28
Bilirubin, mg. per 100 c.c.*	1.5	5.9	4.5	9.0	1.5→4.0
Cephalin flocculation	Neg.	—	3+	Neg.	2+
Thymol flocculation	—	—	—	—	1+
Thymol turbidity	—	—	—	—	1.0
Bromsulphalein retention, per cent	6 (40 min.)	16 (40 min.)	—	28 (45 min.)	4 (45 min.)
Prothrombin, per cent of normal	100	—	70	94	100
Serum albumin, g. per 100 c.c.	4.4	—	—	4.6	5.0
Serum globulin, g. per 100 c.c.	3.0	—	—	3.0	2.3
Total protein, g. per 100 c.c.	7.4	—	6.3	7.6	7.3
Cholesterol, mg. per 100 c.c.	208	—	—	—	109
Alkaline phosphatase, Bodansky units	—	—	—	—	4.5
Urine urobilinogen	1:20	1:40	1:50	1:32	1:80
Urine bilirubin	Neg.	Neg.	Neg.	Neg.	Neg.
Bone marrow	Normal	—	Normal	—	Normal
Fæcal urobilinogen, mg. per 24 hours	—	—	—	—	180

*Normal value of bilirubin 0.1 to 0.2 mg. per 100 c.c.

Comment.—It is to be noted that the laboratory studies disclosed no liver dysfunction except the hyperbilirubinæmia and that no suggestion of a hæmolytic process was found. The only constant abnormality was bilirubinæmia and mild icterus. The father's blood was studied and showed a normal amount of bilirubin.

CASE 2.—A 28-year-old housewife first came to the clinic in 1943 complaining of fatigue of one year's duration. She had had jaundice for 13 years but had not been ill during this time. Two brothers had also had jaundice for many years although this had not interfered with their normal hard physical work. No other relatives had been icteric to her knowledge. Physical examination showed no hepatomegaly or splenic enlargement. The only abnormality was mild icterus of the skin and scleræ.

Table I gives the laboratory findings. The bilirubin excretion test showed marked delay in excretion with a fasting bilirubin level of 6 mg. per 100 c.c., which after the injection of 50 mg. of bilirubin intravenously immediately rose to 9 mg. and stayed at that level for the following three hours. Both glucose and galactose tolerance tests were normal.

Four years later, in 1950, she was admitted to another hospital because of incomplete abortion and at that time her physical examination was again essentially normal except for jaundice. The liver and spleen were not palpable, the blood counts were normal and the red blood cells were normally fragile in hypotonic saline solution.

Comment.—This patient was known to have had jaundice for a total duration of 20 years and had a family history of a similar asymptomatic jaundice in two of her brothers. There was no suggestion of hæmolytic disease. The increase in bromsulphalein retention on two occasions and the decreased prothrombin on one occasion made the diagnosis somewhat doubtful. However, careful evaluation of the over-all picture, together with the family history of two chronically jaundiced brothers, in whom brief studies showed no hepatomegaly or splenomegaly and no bilirubinuria, is suggestive of constitutional hepatic dysfunction. Her chronic fatigue improved when certain home problems were adjusted and there was nothing in her subsequent history to suggest that the fatigue was related to the liver abnormality.

CASE 3.—This 15-year-old boy was admitted because of known jaundice of eight months' duration. He had no complaints and was physically active in sports and other extracurricular activities. Physical examination was normal except for a slight icteric tinge in the scleræ and a palpable splenic tip. The liver was neither enlarged nor tender. There was no history of exposure to hepatotoxic agents or of jaundice in his neighbourhood. The family history was negative. His laboratory and roentgenographic reports are shown in Table I. There was no evidence of excessive blood destruction or of abnormal liver function.

Comment.—This case illustrates an instance of long-standing clinical jaundice associated with hyperbilirubinæmia and splenomegaly. The enlarged spleen is an unusual finding in this condition but the literature occasionally refers to such cases.

SUMMARY

Three cases of persisting jaundice falling into the pattern of constitutional hepatic dysfunction have been reported. It is important to consider this abnormality when the physician is confronted with jaundice that is unassociated with other evidences of liver disease.

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SPONTANEOUS RUPTURE OF UTERUS IN SECOND TRIMESTER OF PREGNANCY*

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SPONTANEOUS RUPTURE of the antepartum uterus is uncommon in the first and second trimesters. Nevertheless in 1903, Baisch was able to record 37 instances of non-traumatic uterine rupture which occurred in the first six months of pregnancy.[2] These were associated with congenital malformations of the uterus, pathological implantation of ova, inflammations, neoplasms and previous Cæsarean section, or occurred without discoverable cause. Improved obstetrical and gynæcological practice may partly explain the paucity of more recent reports, which precludes the potentially useful contrast of early spontaneous uterine rupture with that occurring at or about full term under conditions of modern medical practice. In these few reports, spontaneous uterine rupture in the first and second trimesters, as later in pregnancy, has been reported as a sequel to Cæsarean section[1, 5, 14] and to other operations which may be supposed to lead to scars in the myometrium.[9, 11] Puerperal endometritis,[13] bicornate malformation[6] and leiomyomata[15] have also been associated

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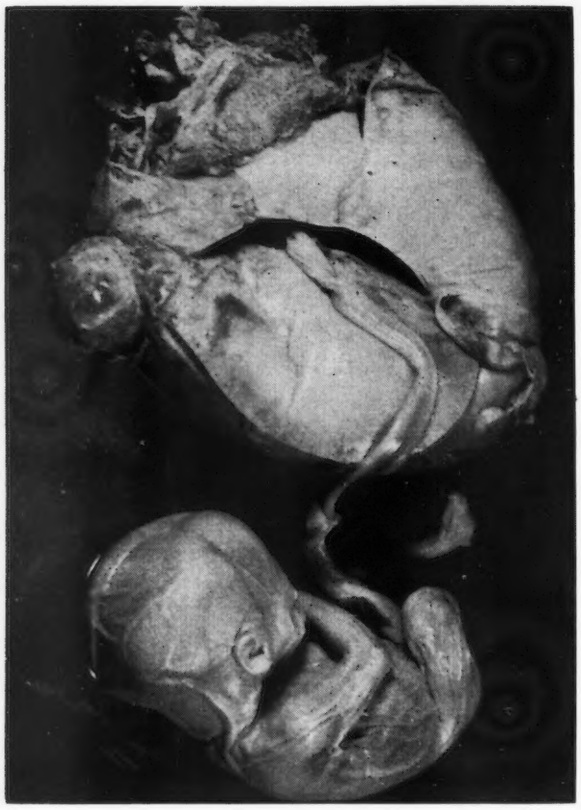

Fig. 1.—Hysterectomy specimen showing fetus extracted through flap made in the left lateral aspect of uterine corpus. Note herniation of placenta and fetal membrane through complete rupture of antero-inferior corpus wall.

with this catastrophe. In one report, with autopsy findings, a spontaneously ruptured uterus showed no pre-existing lesion.[12] The following instance of complete spontaneous uterine rupture occurred in the fifth month of pregnancy in the margin of the scar resulting from classical Cæsarean section for Couvelaire uterus.

The patient was a 33-year-old white gravida V, para IV. The first three pregnancies were uneventful and terminated in normal deliveries. The fourth pregnancy was terminated at the 34th week because of abruptio placenta with retroplacental hæmatoma and hæmorrhage into the wall of the uterus (Couvelaire uterus) when on August 4, 1953, a classical Cæsarean section was carried out. The baby was stillborn. The mother made an uneventful recovery.

The fifth pregnancy was diagnosed on March 22, 1954. The last menstrual period began January 15, 1954. Prenatal examinations in March and April disclosed nothing remarkable.

On June 6, 1954, the patient suffered a sudden dull lower abdominal pain while at stool about 8.00 a.m. She felt weak and returned to bed where the pain became worse and radiated to both flanks. She recalled that when she attempted to stand her vision became blurred. She developed sharp pain in the epigastrium and in the right shoulder. Vomiting, profuse perspiration and chills ensued. When she was seen at home about 10.00 a.m., shoulder pain was pronounced, the inferior abdominal quadrants were rigid and tender, there was shifting dullness in the flanks, blood pressure was 80/10 mm. Hg and pulse rate 110. The patient was admitted to hospital about 11.30 a.m. On vaginal examination, manipulation of the cervix caused severe pain. The patient was immediately prepared for blood transfusions and emergency laparotomy was begun about 1.00 p.m.

On opening the peritoneum, an estimated 2000 c.c. of fluid and clotted blood was found in the peritoneal space. The uterine enlargement was consistent with 4½ months' gestation. In the antero-inferior aspect of the uterine corpus there was a roughly circular rent an estimated 7-8 cm. in diameter. Through this opening protruded placental tissue and fetal membranes. Both oviducts and ovaries were unremarkable. A total hysterectomy with left salpingectomy was carried out. Two units of blood were given during this procedure, and two more immediately afterward. Blood pressure levels rose progressively until normal levels were reached in the early evening.

Postoperative recovery was prompt. A hæmoglobin level of 8.8 g. % was reported on the second postoperative day. The patient was discharged from hospital on the ninth postoperative day.

Pathology

The hysterectomy specimen comprised a pregnant uterus with cervix and left oviduct weighing together 1100 g. Anteriorly and to the left of the midline, the inferior portion of the corpus showed a circular defect measuring 7.5 cm. in diameter. Through this defect herniated a sac of fetal membranes and placental tissue (Fig. 1).

For a distance of 2.5 cm. to the right of this defect, the midline myometrium measured only 0.3 cm. in thickness. Almost immediately to the left of the defect, the mural thickness was 0.7 cm., which was the average mural thickness well above the defect and in the posterior wall. Sections of the thin portion of the anterior uterine wall were embedded in paraffin and stained by hæmatin, phloxine and saffron, by Mallory's and van Gieson's techniques for connective tissue, by silver impregnation for reticulum, and by Weigert's technique for elastica. These showed a thin peripheral layer of smooth muscle, lined by a narrow zone of fibrous connective tissue (Fig. 2). The latter was relatively acellular and was made up of dense collagen fibres and abundant reticulum.

The placenta was implanted centrally upon the anterior uterine wall, and chorionic villi in areas impinged directly upon thin and fibrosed myometrium, where decidua was present inconstantly, and in layers only a few cells thick (Fig. 2). The placenta was otherwise unremarkable. In no area did placental villi penetrate to an appreciable depth beyond the level of the decidua. The umbilical cord was

attached centrally. The 430 g. male fetus was well developed.

Spontaneous and complete uterine rupture had occurred at the margin of a thinned out scar in the antero-inferior corpus myometrium. This scar was consistent in character with a scar resulting from Cæsarean section. Signs of old and incompletely resorbed hæmorrhage were not found.

DISCUSSION

The combination of abdominal pain with signs of hæmoperitoneum and shock coming on in the latter half of pregnancy should suggest complete spontaneous uterine rupture. Blood loss with shock is likely to be severe,[6, 7, 11-13, 15] as exemplified in this case by the finding of an estimated 2000 c.c. of blood free in the peritoneal space. Replacement of blood loss with control of shock and control of bleeding by repair of the uterus or by hysterectomy[4, 7] are mandatory and urgent. Unrecognized cases are usually fatal.[4, 5, 12]

In addition to Cæsarean section,[1, 5, 14] salpingectomy[11] and curettage[9] have preceded spontaneous uterine rupture in the second trimester. Postoperative scars of the myometrium undoubtedly impair the resilience and tensile strength of the uterine wall. In the case reported here, the myometrial scar stretched out and became thin, and eventually pulled away along one margin.

Interestingly, lower segment uterine rupture, as opposed to rupture involving the fundus more superiorly, is reputedly more characteristic of labour than the antepartum state.[7] The uterine rupture described here evidently involved only the inferior end of a classical Cæsarean section scar. The same general area of uterine wall would have been incised in a vertical low-segment Cæsarean section. While liability to uterine rupture in pregnancies subsequent to classical Cæsarean section is often given as one reason for favouring low-segment Cæsarean section, instances of uterine rupture following the lower segment operations have been recorded.[3, 5] Technique in repair rather than the site of Cæsarean incisions may be implicated in subsequent uterine rupture. The value of careful technique in repairing Cæsarean incisions[5] and the employment of the transverse low segment incision[3] have recently been emphasized as a means of avoiding post-sectional uterine rupture.

It has been pointed out that placental implantation upon a post-Cæsarean scar favours subsequent rupture.[5] In the case reported here, indeed, the placental implantation centered precisely over the myometrial scar. There was, however, no considerable trophoblastic invasion deep to the decidua such as might have been expected if, earlier in pregnancy, the decidua basalis had been defective.[10] The discontinuity of the decidua that was found in examining the hysterectomy specimen is reasonably explained as a result of the stretching and thinning of the uterine wall adjacent to the point of rupture.

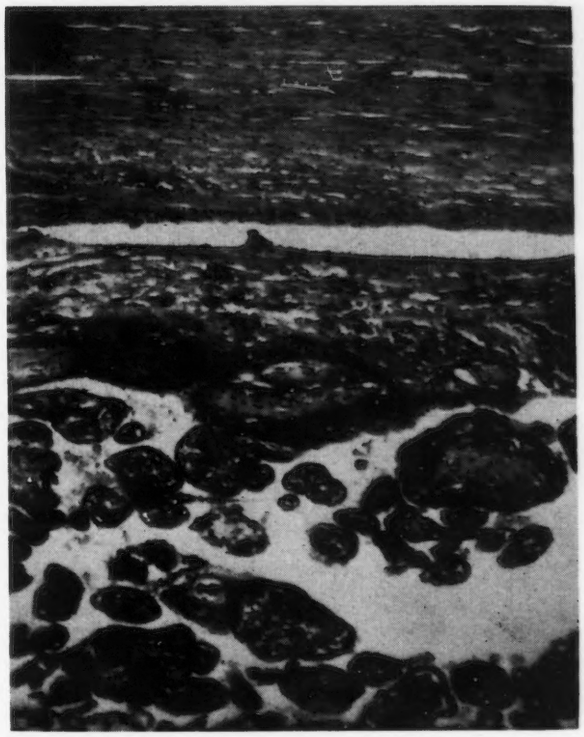

Fig. 2.—Section of uterine wall to the right of the point of rupture. Note thinning out and discontinuity of the decidua, but absence of intrusion of trophoblastic elements into the thinned uterine wall. × 75.

The retroplacental and intramural hæmorrhage that led in this case to Cæsarean section may have contributed to the extent of postoperative myometrial scarring. The subsequent uterine rupture may thus favour the acceptance of such hæmorrhage as an indication for more immediate hysterectomy in cases of this nature.

SUMMARY

A case of spontaneous uterine rupture occurring in the 5th month of pregnancy at the margin of a scar resulting from a previous classical Cæsarean for Couvelaire uterus is presented. Diminished tensile strength of the uterine wall resulting from postoperative scarring is implicated as an important factor leading to this catastrophe. The role of retro-

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placental and intramural hæmorrhage in contributing to the extent of postoperative scarring is conjectural, but would favour considering such hæmorrhage as an indication for hysterectomy.

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MALIGNANT FIBROUS MESOTHELIOMA OF PERITONEUM*

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A REVIEW of the literature in 1954[1] disclosed eleven cases of peritoneal mesothelioma, to which Stout has added a list of some 117 cases collected at Columbia University over a 30-year period.[2] The tumour has been classified as solitary or diffuse in gross presentation, and fibrous or tubular in histological appearance. The pattern histologically varies over a wide range because of the multipotential-cell origin of the lesion.

The cardinal symptom appears to be recurring ascites with associated abdominal discomfort. Pain, weight loss and the symptoms of bowel obstruction are late phenomena. The condition has usually been rapidly fatal, although a few cases have responded to x-radiation therapy[1-5] and more recently to intraperitoneal radioactive gold.[4] Nitrogen mustard chemotherapy was of no demonstrable benefit in a case similar to the one presented here.[3]

The purpose of this paper is to present a case in which an extremely large tumour was discovered as an incidental autopsy finding, apparently without serious symptoms.

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Clinical Summary

An 83-year-old white man was admitted to the Royal Alexandra Hospital, Edmonton, Alberta, on March 30, 1956, as a medical emergency, because of acute dyspnœa.

The patient, a retired old-age pensioner, had been in fairly good health for his age, prior to his terminal admission. There was a history of moderate shortness of breath, but this had not interfered with his hobbies of gardening and walking. There had been no recent weight loss, his appetite had been good, and aside from some constipation and occasional nocturia and hesitancy, his functional history was entirely negative. The past history elicited a few bouts of pneumonitis and two admissions for traumatic lesions as a young man.

He was obviously dyspnœic but in no pain. The neck veins were distended and his carotid pulse was visible. The fundal vessels were tortuous and showed some nicking. The ocular reflexes were normal. There was an irregularity of his pulse at 76, a B.P. of 160/60 mm. Hg and moderate pitting œdema of the ankles, sacrum and back. The liver edge was palpable four fingers'-breadths below the right costal margin. The heart sounds were distant, and a rough systolic aortic murmur was present with radiation into the neck. Posterior basal rales were present over both lung fields. The abdomen was very protuberant and dull to percussion, and the umbilicus was everted. The prostate was firm, and classified as a Grade II hypertrophy. The provisional diagnosis on admission was arteriosclerotic heart disease with calcific aortic stenosis and right heart failure.

A chest radiograph shortly after admission showed a cardio-thoracic ratio of 17.5:33 cm., with slight congestion of the hilar shadows. A scout plate of the abdomen showed some distension of colonic loops in the left upper abdomen but no gross dilatation of large or small bowel. No fluid level or subdiaphragmatic air was seen. A barium enema was normal.

On admission, an electrocardiograph showed left bundle branch block and controlled auricular fibrillation. A repeat ECG showed only fibrillation with frequent ventricular extrasystoles, probably associated with extensive myocardial damage and digitalis effect.

Laboratory examination revealed an Hb. level of 11.3 g. %, a hæmatocrit value of 36, and a corrected Wintrobe sedimentation rate of 21 mm. per hr. The white cell count was 12,800 with 87% neutrophils. Several urinalysis showed a specific gravity of 1.012-1.020 with a trace to 3 plus protein, no sugar and many hyaline casts. The total serum protein was 6.6 g./100 ml. with an albumin of 3.4 g./100 ml. and a globulin of 3.2 g./100 ml. The serological test for syphilis was negative.

The patient was digitalized with Purodigin and placed on Thiomerin and ammonium chloride ther-

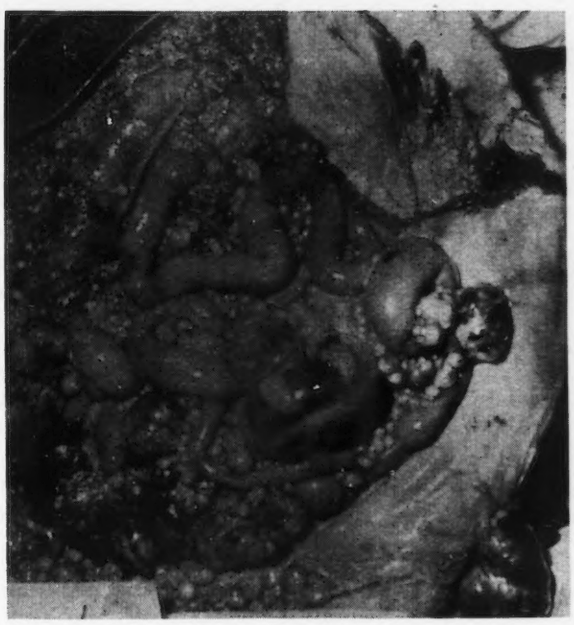

Fig. 1.—Mesothelioma of peritoneum—myriads of sessile and pedunculated tumour masses involving the superficial aspects of parietal and visceral peritoneum.

apy. A paracentesis was attempted but no fluid was obtained. The acute dyspnœa present on admission cleared initially, but he developed recurring episodes of acute pulmonary œdema and died in one such attack on the tenth hospital day.

Anatomical Findings

At autopsy the stigmata of long-standing hypertensive and arteriosclerotic heart disease, including a 600-gram heart showing marked left ventricular hypertrophy and a good deal of interstitial myocardial fibrosis, were found. In addition chronic passive congestion of lungs, liver and spleen with terminal acute pulmonary œdema was present.

The interesting feature was an incidental finding. When the peritoneal cavity was opened, approximately à litre of straw-coloured fluid was found, together with myriads of sessile and pedunculated tumour masses (Figs. 1 and 2). These were present on the visceral and parietal peritoneum and varied in size from less than one millimetre up to 4 cm. in diameter. The nodules were solid except for obvious areas of hæmorrhage and necrosis and none appeared to penetrate the wall of the intestine or the capsule of any of the abdominal organs. A careful search for a primary lesion was carried out with no success. The only other lesion demonstrated was advanced melanosis coli (Fig. 2). All tumour masses were confined to the peritoneal cavity.

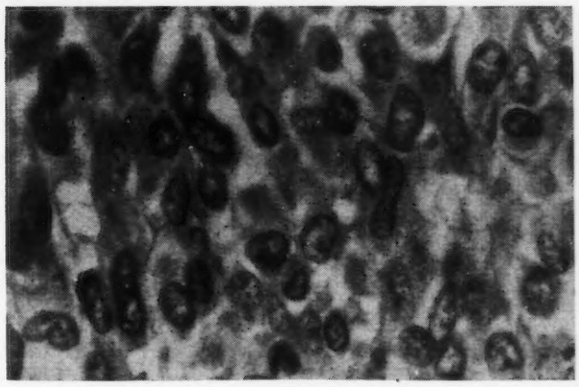

Fig. 3.—Fibrous mesothelioma of peritoneum (×620).

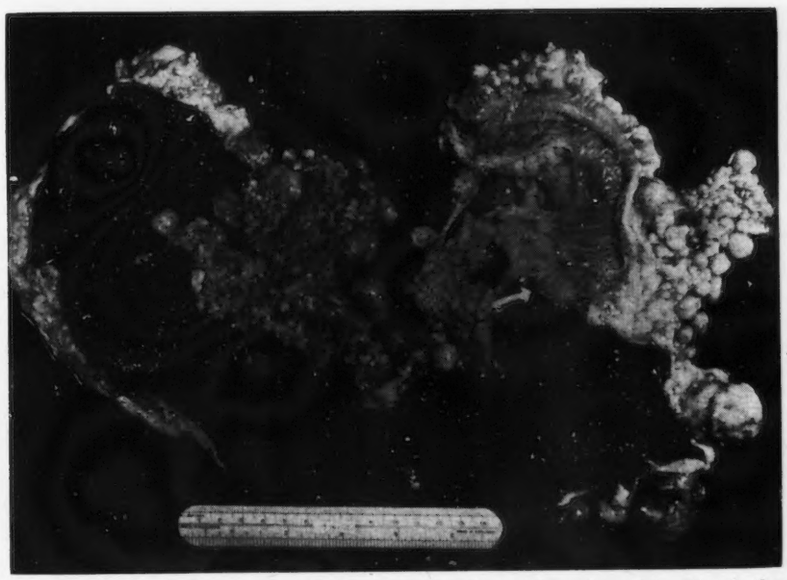

Fig. 2.—Peritoneal mesothelioma and advanced melanosis coli of the ileocæcal junction.

Histologically the tumour from the peritoneum showed a fairly uniform pattern of elongated spindle-shaped cells (Fig. 3) arranged in solid masses, whorls and palisades with numerous areas of œdema and hæmorrhage. The individual cells had spindle-shaped nuclei which contained prominent chromatin granules. The cytoplasm was pale and eosinophilic and streamed into a moderately vascular interstitium. Mitotic figures were rare and no tumour giant cells were seen. There was no evidence of epithelial tissue in any of the sections. The pattern was remarkably constant.

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The histological interpretation was diffuse pedunculated fibrous mesothelioma of peritoneum—probably malignant.

DISCUSSION

Recently a number of cases of pleural and peritoneal mesothelioma have been described, including solitary and diffuse forms, and the response to radiation particularly with radioactive gold has been encouraging.[4] The cases which have improved by therapy have all been of the "tubular" or "mixed" type and presented with effusion. As late as 1956, Ackerman[6] had not seen a good example of a "diffuse fibrous mesothelioma" and the rarity of the lesion prompted this case report. It is interesting that the massive peritoneal involvement in this case should have been present without recurring ascites and with no symptoms apart from slight abdominal distension which was due largely to an enlarged liver and heart failure rather than to the multiple tumour masses. A similar case reported by Hill[3] was interpreted as a solitary tumour with metastases, but we feel that in the case presented here it is impossible to say that any particular lesion was primary.

SUMMARY

A case of diffuse fibrous mesothelioma is presented. The tremendous peritoneal lesion was associated with no clinical symptoms, and was an isolated incidental finding at autopsy.

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CANDIDATES FOR DISEASE

"It has long been known that we must take into account not only the agent, whether it is an infectious organism, a poison, a dietary fault, a physical strain or some other external factor, but also the person or host himself. Yet we have paid in large part only lip service to this internal factor of heredity. We have hardly tried as yet to select from the mass of mankind the individuals who are to a greater or lesser degree candidates for any particular disease, to direct, as of course we should, our special programs of preventive medicine at them, thus avoiding a great waste of time, of money and of energy."—P. D. White, *New England J. Med.*, 256: 964, 1957.

Special Article

OBSERVATIONS ON MATERNITY CARE OVERSEAS

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IN THE SUMMER of 1956 I had the privilege of visiting Britain and the Scandinavian countries to learn something of maternal and child health services in England, Scotland, Denmark, Norway, Sweden, Finland and the Netherlands. The principal focus was on the observation of public health or preventive services. These countries were selected because their favourable maternal and infant mortality rates indicated that they enjoyed a high level of maternal and child care. The trip was very interesting because of the contrasts in point of view and in the provision of care, and reassuring because of the similarities.

In general there were more striking differences in the provision of maternity care than in child care. There were at least two obvious reasons for this. The first major difference was the presence of trained midwives or nurse-midwives in the field of maternity care. The second contrast was the wide acceptance of prenatal health supervision as a responsibility of public health services. This was manifested by the fact that in most countries prenatal care was readily available in every community, often in clinics organized by the local health department.

It would be difficult to indicate in a few words the key role which the trained midwife played in all phases of maternity care. With her excellent training in all phases of the normal maternity cycle and her responsibility to observe and refer to the physician all deviations from the normal, she was in a position to make a unique contribution to the health supervision, health education, support, and encouragement which are the main health needs of the majority of expectant mothers. One had the feeling that the very presence of the trained midwife in the community helped to remove maternity care somewhat from the field of therapeutic medicine, though never so far that all the resources of therapeutic medicine were not available for the management of complications. There seemed to be more emphasis on the normality of pregnancy which, though it is a period of physiological stress, should not be considered one of abnormality.

The duration of midwifery training varies from country to country, from 18 to 36 months. There seemed to be a tendency to co-ordinate the training of nurses and midwives to produce nurse-midwives. I was reminded more than once

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that midwifery training antedated nursing training by many years and that the midwife was sometimes understood and accepted in the community more readily than her more recent colleague, the public health nurse.

The pattern of the provision of prenatal care was in contrast to the pattern on this continent. In a number of countries visited a high proportion of women received prenatal health supervision at maternal and child health centres which were a part of the local public health service. The proportion of women receiving prenatal supervision under these auspices ranged from 50% to 70%. Prenatal clinics would be attended by physicians, midwives and sometimes public health nurses. In addition prenatal care could be obtained in prenatal clinics in hospitals with large obstetric services and from private physicians. Arrangements varied for the provision of specialist consultation at prenatal clinics. In Britain obstetrical consultants from local hospitals were made available to local public health clinics. In Norway it was emphasized that community clinics were for normal expectant mothers. Those with complications were referred to specialists or to hospital clinics. As in Canada, the availability of obstetrical specialists for consultation was limited in rural areas.

In Britain it was stated that since the inauguration of the national health service there had been some decline in attendance at public health prenatal clinics and more use of the family physician to provide maternity care. In one city visited close working relationships had been worked out between the local health department and the general practitioner obstetricians to enable the mothers to continue to receive the additional supervision of midwives and benefits of group education. One-third of these practitioners saw their own prenatal patients in local authority clinics with midwives and other staff in attendance. In another city an arrangement had been made with a group of five practitioners whereby they would see their prenatal patients on a particular afternoon, with the local health department midwife in attendance. Such programs seemed to hold real promise for the improvement of the total care of mothers and the furthering of the mutual understanding of health workers and private physicians regarding their complementary roles in this field of health care. In Denmark the program for health care of pregnant women differed. By the Pregnancy Act of 1945 mothers were entitled to three visits to a physician and seven to a midwife, the cost of which was borne by the state. About 75% of women availed themselves of these services. The Netherlands had fewer organized services for prenatal care. The usual pattern was for mothers to obtain their care directly from midwives and private physicians.

These prenatal services were extended into the home, through the home visiting program of the midwives. Home visits might be made if the mother failed to keep her appointment, to follow up a minor abnormality which had been noted at the clinic, or for health supervision and instruction.

In most countries there was considerable interest in prenatal education and preparation for labour, though the programs were of fairly recent development. This teaching was done in maternal and child health centres or prenatal clinics of hospitals by midwives, physiotherapists, and sometimes public health nurses. In Britain the exercise and relaxation phases of the program were often taught by physiotherapists and it was considered important that midwives receive their instruction in exercises and relaxation from physiotherapists. It seemed somewhat of a contradiction to encounter as much enthusiasm and interest in preparation for labour in countries where labour had always been reputed to be much more natural, less "interfered with", than on this continent.

Care at confinement was also shared by midwives and physicians, whether confinement took place at home or in hospital. The proportion of home confinements varied but, except in Sweden, where 97% of women were confined in hospital, the proportion of women confined at home was higher than in Canada. Our rate of 14% home confinements is influenced mainly by home deliveries in three provinces, Quebec, New Brunswick and Newfoundland. Only in the Netherlands, where 78% of confinements occurred at home, was the ratio reversed. In most other countries the trend towards hospital confinement seemed to have the support of obstetrical authorities though it was influenced by other factors, such as the availability of maternity beds and a long tradition of home confinement. In areas of bed shortage, primiparæ, women with previous difficulties and grand multiparæ were given priority. There always appeared to be beds for the admission of complications and I was impressed in Britain particularly with the high proportion of maternity beds set aside for the admission of prenatal complications, notably toxæmia.

The traditional role of the midwife has been the provision of intrapartum and postpartum care at normal home confinements and she still fulfilled this important function in a high proportion of home confinements. It was emphasized repeatedly that the midwife always worked under the supervision of a physician and was obliged to call him if any abnormality was noted. Also, if the physician had indicated his wish to attend the confinement himself, the midwife notified him and remained to assist. Even in hospital maternity services midwives attended normal confinements, though in that setting under more direct supervision of physicians. Nowhere did I encounter any serious dissatis-

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faction on the part of physicians with this shared responsibility for maternity care. The view was expressed in Britain that the trend towards hospital confinement, in narrowing the midwife's traditional field of home confinement, would probably result in a somewhat different working relationship between the two professions.

The physical facilities of maternity hospitals were not unlike our own. One difference was that the labour and delivery room were often one and the same, the place where the spontaneous delivery took place. Special operating-delivery rooms were set up but used only for unusual complications, such as forceps application, episiotomies or Cæsarean sections.

What little I had heard of newborn hospital care overseas had led me to expect rooming-in or the care of mother and baby together to be the usual pattern. This did not prove to be so in the large maternity hospitals visited. However, in England several hospitals visited used this method and there was considerable interest in it. A memorandum from the Ministry of Health, December 1955, to all hospital authorities had drawn attention to the advantages of this method of care, and recommended its adoption in all maternity services. In Denmark babies were said to be kept with their mothers frequently and I was told that a study was being made in one hospital to enable the mothers to participate more in the babies' care. In Finland a new maternity hospital to be built for the national school of midwifery was expected to provide some rooming-in facilities. One physician on the Continent with whom this matter was discussed expressed the view that the universal acceptance and success of breast feeding went a long way towards developing and strengthening the mother-child relationship which rooming-in is designed to foster.

The incidence and success of breast feeding was a subject frequently discussed. In almost all countries visited there was some anxiety expressed regarding its decline. It was apparently a much more acute problem in Britain than in Scandinavian countries. In the latter, mothers apparently accept their responsibility to nurse their babies as a matter of course, and the establishment of breast feeding seemed to present no great problem. Difficulties arose most frequently when mothers returned to work outside the home. This was also a major factor in Britain but there also seemed to be a problem of maternal attitude there, such as is encountered here.

Postnatal medical care was available under much the same auspices as prenatal care. The impression was gained that overseas mothers, like our own, did not always appreciate the importance of postpartum examination and seek it.

In some countries family planning advice was available at postnatal clinics or through special clinics of the local health authority. In the Scandinavian countries legislation existed to provide for the termination of pregnancy in the presence of certain precisely defined medical or sociological conditions.

It was interesting to find considerable direct assistance provided for expectant mothers in addition to medical care. This consisted of financial grants in Sweden and the Netherlands, nutrition supplements in Britain and Denmark, and a gift of clothing or equivalent funds in Finland. These were in addition to grants or insurance payments to working mothers. The tangible benefits of these subsidies were not easy to assess. However, such forms of assistance like the provision of medical care all served to draw attention to the needs of expectant mothers and helped to maintain the status of maternity in the community—a status that is perhaps higher than it is here.

CONCLUSIONS

Regardless of one's attitude towards the provision of prenatal medical care by public health authorities there seemed little doubt that in the countries visited this participation had resulted in a better distribution of maternity care outside of cities and made it more accessible by removing the financial barriers.

There are indications in some parts of our country, in terms of excessive maternal, neonatal and stillbirth rates, that all women are not receiving adequate care. An objective study of maternity care in some of these areas would be very interesting in evaluating the relative importance of economic factors, the availability of services and the mother's own attitude towards her need for medical and nursing care during pregnancy.

Though it is difficult to present tangible evidence to support the idea, a comparison of maternity services overseas with our own suggests that there may be room for some reorientation of the attitude of everyone in contact with the expectant mother towards the normality of the event in most instances. Along with this there should perhaps be a wider appreciation of the mother's need for information about herself and the care of her baby so that she can better understand the reasons for some modifications to her routine of living and be prepared for the responsibilities of parenthood. Delivery in hospital, an institution geared to do something quickly and efficiently for the sick person, has probably contributed to an attitude of wanting to do something quickly and efficiently for this other member of the community who is not sick, but in normal labour. She has usually not come to the hospital to be treated, but because it is the safest environment for her to carry out her task of delivery with the encouragement and careful supervision of nurses and doctors.

It seems that the total health care of expectant mothers could be strengthened by better understanding and fuller co-operation between physicians and public health workers of both official and voluntary agencies. This could begin with stronger physician's support for the organized programs of prenatal teaching which have developed in many parts of Canada in recent years. The kind of support most readily understood and appreciated is, of course, referral of patients. These prenatal classes have been received with enthusiasm by parents and physicians in many communities. All the evidence indicates that they make a real contribution to the establishment of this concept of normality and alleviate many fears and anxieties of both mothers and fathers regarding pregnancy and the care of babies.

In many instances there is need for individual nursing supervision and teaching which can be carried into the home. A home visit by a public health nurse to a poor attender, or a mother too anxious at her first office visit to really listen to the doctor's advice, has been shown to be a very useful means of introducing sound advice into the home. Too, a visit to a toxic mother between office visits can give the doctor valuable information about her home problems and her understanding of his instruction to rest, restrict her diet, and so forth.

To remove any suggestion that lack of understanding is all on the part of physicians, it should be added that public health agencies have not always been as aware of the total health needs of expectant mothers, or visualized their educational and supportive role in the provision of maternity care.

Regardless of the past, there is much evidence of the growing interest of all health agencies in prenatal teaching and nursing supervision. There are, no doubt, a number of factors contributing to this change in attitude. One is the fact that a real effort is being made to prepare both public health and hospital nurses for this developing field of health education through special courses and institutes. The enthusiasm with which this preparation is being received suggests that nursing training for maternity care may not be adequate to prepare nurses for the broader supportive and educational role which they are being called upon to play in this field. And finally, I feel it would be unfair not to suggest as well that the thinking of practising physicians and the obstetric teaching of physicians at various stages of their development might be further orientated towards the normality of pregnancy and the needs of the mother for information and support, in addition to expert medical supervision and management of complications.

SUMMARY

Observations of maternity care overseas have been recorded and similarities and contrasts between their services and our own have been described. Two essential differences were noted. One difference was the participation of public health authorities in the provision of prenatal and postnatal care, thereby emphasizing the normality of pregnancy and its preventive medical aspects. The second difference was the prominent role played in prenatal, intranatal and postnatal care by the trained midwife, and her particular contribution in fulfilling the supportive, health supervisory and educational needs of expectant mothers. Similarities in the provision of care at confinement were noted, particularly the trend in most countries towards hospital delivery. The provision of assistance to mothers other than medical care such as grants, nutrition supplements or employment leave has been described. The implications of these differences and similarities for maternity care in Canada have been suggested.

SHORT COMMUNICATIONS

AN OUTBREAK OF ASIAN INFLUENZA IN A GIRLS' CAMP*

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THE CENTENARY WORLD GUIDE CAMP was held from August 8 to 19, 1957, at Doe Lake, 20 miles northwest of Huntsville, Ontario. Forty-six countries had sent their representatives, bringing 1496 guides and guiders to Ontario. A group of 30 rover scouts was stationed in a camp close by to help with the heavy work, and a group of about 70 people consisting of telephone operators, press and movie people, bankers and policemen brought the total camp population up to 1600. For administrative purposes the camp was divided into four subcamps—Mic-Mac, Iroquois, Cree and Bella Coola. The headquarters building and the infirmary were in the centre, and west of these was a log cabin, called Sunset, housing all the people responsible for the waterfront. The rover scout camp was approximately a mile west of Sunset. The youngest guide was 15, the oldest guider 71. Only about 8% of the camp population slept in houses, the rest being in tents. During the daytime the weather was fine but at night it was cold, the temperature often falling to freezing point; on many mornings fog was very heavy.

In this very isolated community an illness broke out; it was called at the time "the flu" and necessitated hospitalization of 11.5% of the camp population in a few days. Only 15 of these patients had a nasopharyngeal irrigation done,

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TABLE I.

Maximal temperature 100° F.	15.1%
Maximal temperature 101° F.	22.7%
Maximal temperature 102° F.	34.6%
Maximal temperature 103° F.	7.5%
Fever for one day	32.9%
Fever for two days	53.5%
Fever for three days	13.6%

but the Asian influenza virus was cultured from 6 of them and it is likely that most, if not all, of these patients had Asian influenza.

All patients had fever, headache, general malaise, sore throat, aching all over and a feeling of tightness in the chest; 50% of patients developed all or some of these symptoms 8-24 hours before they developed fever. Table I analyzes the duration and level of fever for the 185 cases of influenza occurring at Doe Lake.

Those who were febrile for three days presented in most instances with a different clinical picture, and either had secondary infections or may not have had Asian influenza to start with.

TABLE II.

Age group	*Total camp population*	*% of total camp population*	*Total number of sick campers*	*% of sick campers*
15 - 19	1198	74.8%	158	85.4%
20 - 29	144	9.0%	14	7.6%
30 - 39	137	8.6%	10	5.4%
40 & over	121	7.6%	3	1.6%

The temperature curve had its peak almost invariably from noon to 4 p.m. The fever was in many cases higher on the second day than on the first and always fell by crisis. Pulse rates were high with the fever and about 34.6% of all patients had persistent tachycardia of between 100 and 120 for 24 to 36 hours after their temperature had returned to normal. Blood pressure was normal in all cases where it was checked.

Patients were acutely ill and had a great need for sleep, but only about 10% were actually drowsy. All complained of sore muscles and backs, but only two or three had actual muscle spasm for a day or two. No one developed meningeal signs. Ten per cent had a conjunctivitis. All had throat findings. In most instances the soft palate was pale and swollen, the uvula injected and œdematous, the posterior pharyngeal wall dry, injected with beefy red lymphoid tissue protruding in papules and plaques. The cervical lymph nodes were not enlarged. These findings persisted for several days. Dark red congested throats, ulceration and exudate were less commonly seen, and were usually associated with a prolonged fever and a mild cervical adenitis. Seventy per cent had a laryngitis and were often still quite hoarse when leaving camp. Stuffiness of the nose was a very common complaint and the nasal mucosa was swollen in most instances. About 20% complained of diminished hearing, but there was an absence of physical findings. Although 40% had a very severe spasmodic, unproductive cough not responding to codeine, there were practically no chest findings on physical examination. Only a few cases presented with bronchial breathing but after one day the breath sounds were normal again. One girl was admitted to hospital at the end of camp, because of bronchial breathing, but her chest radiograph was negative. The seven girls out of 185 who developed wheezing gave a history of previous attacks of asthma; these were very sick and the condition was difficult to control. Nausea at the onset of the disease was not uncommon but vomiting occurred only in five cases (less than 3%). The whole group was treated with aspirin and prophylactic sulfonamides and so far no complications have been reported.

Table II gives a breakdown of the camp population into age groups and the attack rate of the disease in the different decennia. The disease affected the younger campers far more than the more mature group.

It took a few days to realize that the camp had been struck by an epidemic as the onset was quite insidious; this becomes evident in Table III. One week before the official opening 375 guides from all over Canada had been at camp and no illness had occurred. The rest of the campers arrived on August 8, bringing the total population up to 1600. The official camp opening was on August 9.

The first patient was hospitalized on August 10. This was a guider from Connecticut camping in Mic Mac. On the 12th her friend, another girl from Connecticut but living in Sunset, joined her in the infirmary. On the 13th, these two

TABLE III.—SPREAD OF THE DISEASE WITHIN THE CAMP COMMUNITY

	Aug. 9	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*21*	*22*	*23*	*24*	*25*	
Mic-Mac		1			3	1	7	9	7	10								38
Sunset				1	1	2	1		4	2	1							12
Bella Coola						1	2	17	7	10	2							39
Iroquois							2	16	9	12				2	2	2	1	46
Cree								2	14	15								31
Headquarters								1	3		2							6
Rover Scouts								2	4	2								8
Various groups									5									5
Total		1		1	4	4	12	47	53	51	5			2	2	2	1	185

TABLE IV.

Country	*Total of campers*	*% of total*	*Place of origin of campers with influenza*		*% of total group*	*% of sick group*
Canada	959	59.9%	Ontario	79		
			Quebec	15		
			New Brunswick	4		
			Nova Scotia	1		
			Manitoba	6		
			Saskatchewan	5		
			British Columbia	10		
				120	12.4%	64.8%
U.S.A.	392	24.5%	Connecticut	9		
			New York	4		
			South Carolina	4		
			Florida	7		
			Ohio	1		
			Indiana	1		
			Mississippi	2		
			Arkansas	2		
			Oklahoma	2		
			Texas	1		
			Idaho	6		
			Washington	5		
			Oregon	1		
			California	6		
				51	13.0%	27.5%
Great Britain	44	2.75%		6	13.6%	3.3%
Ecuador	1	0.06%		1	100.0%	0.5%
Surinam	11	0.68%		7	63.3%	3.7%

subcamps had four more new cases. On August 14, subcamp Bella Coola had its first case and the two previously mentioned camps had three more cases. On the 15th the first two guides from subcamp Iroquois had to be hospitalized together with 10 new cases from the first three camps. Until then the total of patients was 22 and they could be nursed in the infirmary. But on the 16th the headquarters building had to be converted into a hospital because the camp had 47 new cases involving all subcamps and including the rover scouts. On the 17th the boathouse was invaded by 53 new patients including five of the non-guide group, and on the 18th the various log cabins all over the camp site were filled with 51 new cases. This was the day of the closing camp fire and on the morning of the 19th most of the guides and guiders left and there were only five new cases. By the 23rd all patients had sufficiently recovered to return to their homes.

Throat irrigations for virus studies were done on eight of the patients on August 20 and the Asian influenza virus was grown from two cases. Surprisingly enough, one of these girls had been sick for four days, the other for three days. The same virus was also cultured from four guides from Surinam who left the camp on August 19, to take hospitality in Port Credit. On August 22, the first two girls of this group developed the previously described symptoms followed by two cases on August 23, two cases on August 24, and one case on August 25.

Throat irrigations were done on the first four patients, with positive results for Asian influenza. Following the contacts it became known that four of the Port Credit hostesses and one guide developed the same symptoms, one hostess on the 23rd and one on the 24th, i.e. five and six days respectively after the Surinam group's arrival in Port Credit. The illness in the hostesses, therefore, occurred one or two days respectively after the first symptoms were manifest in their guests. The other hostesses did not develop any symptoms before August 27. It was interesting to note that of the 46 countries represented at the camp only the members of five groups were affected by the disease. These were Canada, the U.S.A., Great Britain, Ecuador and Surinam. The total number of campers from these countries, the total number of patients in this group and their percentage of the total and of the sick group are shown in Table IV. The complete absence of cases from Central America and most of South America, the West Indies, the European Continent, Pakistan, India, Burma, Ceylon, the Phillippines and Japan is probably explained by the fact that the Asian influenza pandemic had already reached these countries between May and July.

In conclusion, the outbreak of an epidemic of Asian influenza in an international girl-guide camp is described, in which 11.5% of the camp population was hospitalized. Patients were acutely ill at the onset but recovered within five days with only a feeling of weakness left. No serious sequelæ are known.

I am grateful to the Ontario Girl Guide Association and Miss J. Gerow for their help in collecting the data for this paper and also to the Ontario Department of Health for carrying out the virus studies.

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THE FUNCTIONS OF THE HOSPITAL

What should the hospital of the future do? Should it, as some contend, gradually expand its activities until it has taken over the responsibility not only for curative medicine, but for preventive medicine? In other words, should it ultimately become the centre for total medical care of a community? Or should it firmly refuse to be drawn into certain fields of medical activity, traditionally the domain of private general practice?

This is not an academic question. It is a question exercising the minds and thoughts of many medical administrators and public health officers. The entire future of general practice may depend upon the ultimate answer to this question. If anyone doubts the importance of this subject, he should read the report of the technical discussions of the Tenth World Health Assembly, which has now appeared in print (*Chronicle of the World Health Organization,* 11: 198, 1957). The subject of these technical discussions was "The Role of the Hospital in the Public Health Programme", and some two hundred participants attended the sessions under the general chairmanship of Dr. A. J. Metcalfe, Director-General of Health of Australia. Participants were split into nine groups, and the nine group reports were consolidated to make a general statement. It is evident that from the start of the discussions the cards were stacked in favour of an extension of hospital functions, for it is recorded that the groups were all but unanimous (we suspect that dissenters came from this continent) in accepting the definition of a hospital put out in the first report of the Expert Committee on Organization of Medical Care of the World Health Organization:

"The hospital is an integral part of a social and medical organization, the function of which is to provide the population complete health care, both curative and preventive, and whose out-patient services reach out to the family in its home environment; the hospital is also a centre for the training of health workers and for bio-social research."

There is nothing controversial about that part of the report in which the in-patient curative services of a hospital are discussed; the controversy begins when the out-patient department is discussed. Here the participants felt that the extramural activities of the hospital were a practical demonstration of the truth that it should look out beyond its own walls to serve the community. Its functions, they say, should permeate the community through the services of the out-patient department. They then add as a necessary corollary to this that "in this unit the general practitioner attends his patients on equal terms with the other members of the staff, the specialist and the health worker, and he can seek help both in the out-patient department, and, if necessary, in the homes of his patients". It is true that later in the report the suggestion is made that some would consider it a mistake to place the hospital in the centre of the picture when medical care programs are being considered. However, the discussants felt that there was much to be said for a re-orientation of services to transform the out-patient department into a polyclinic. In other words, in a hospital organization there tends to be a shift from hospital beds to out-patient departments.

This is not all. The question of a home care service—especially nursing and midwifery—was considered, although there was a division of opinion on the role of hospital authorities in inaugurating this type of service. There was again a widespread expression of opinion to the effect that the general practitioner should be brought into this health service as fully as possible, and that he should in fact be the keystone of its structure in the smaller units. The general physician, say the reporters, "is in the best position to deal with preventive and curative medicine at the same time and to give health education under his care and to their families."

Many will read this report with uneasy feelings. In the first place, it may be asked whether the concept of one world in medicine has gone

so far that any definite pattern of hospital services can be used without serious modification in all the different types of country. Ought the hospital to function in exactly the same way in Canada and in Saudi Arabia? A highly organized hospital and polyclinic service, such as obtains in the Soviet Union, may be fine for Soviet citizens, but it may be seriously questioned whether Canada either desires or needs such a system.

In Canada, emphasis has been placed on diagnostic services in planning for the universal hospital and diagnostic services program. It is realized, however, that diagnostic services are not necessarily associated with a hospital. Many such services are provided outside the hospital, and it would seem that in the best interests of the community *all* available facilities should be utilized.

Another point on which Canada (and the United States) differs from the majority in practice lies in the supervision of hospital standards. In most countries the state is the authority; we prefer to safeguard our own standards through an independent non-political commission actually referred to in the W.H.O. report. Nothing in Canadian experience has suggested that this function needs to be reassigned, any more than the control of standards of medical education by the medical profession, a system which has worked well.

The other question which arises in everyone's mind concerns the status of the general practitioner. The report pats him on the back repeatedly. He is "the keystone of the structure of the health service"; he is "in the best position to deal with preventive and curative medicine at the same time". Where there is good collaboration between the out-patient department and the general practitioner "the whole facilities of the department, including its laboratory services, increase both the scope and the prestige of the general practitioner's work." What do our British colleagues think of this? In how many areas of Britain is it true to say that "the general practitioner attends his patients on equal terms with the other members of the staff"? Experience in the United Kingdom does not suggest that the pronouncements of the W.H.O. technical discussion groups have received attention. It is this unfortunate gap between theory and practice that the general practitioner will bear in mind when he reads this blueprint for the hospital of the future. In the meantime, he would be well advised to study this report, for it represents the collective thinking of an influential and well-informed group of his professional colleagues.

Editorial Comments

BCG VACCINATION IN CANADA

Probably no topic of current medical interest has been the subject of more prolonged and acrimonious controversy than the question of mass BCG vaccination against tuberculosis, particularly in the United States. Since Canadian medicine tends to follow the American pattern, we in Canada seem to have adopted much of the American attitude on the subject of BCG vaccination, although that attitude is not shared by most other "enlightened" countries, especially on the European continent.

To clear the ground at the outset, it should be stated at once that, in both Canada and the United States, BCG vaccination is recommended only for those who are unavoidably in close contact with individuals suffering from open tuberculosis, or who are otherwise inescapably exposed to that disease. This group includes family contacts, employees in tuberculosis institutions, and physicians, medical students, nurses and laboratory technicians. The current and continuing disagreement is between those who would restrict BCG vaccination to these groups and those who would expand widely the indications for this procedure to include all negative tuberculin reactors in the general population.

An unbiased observer of this controversy, after careful consideration, would probably decide that there was much to be said on both sides of the question. A recent well-reasoned report[1] by the Medical Advisory Committee of Research Foundation in Chicago presents the arguments for and against expansion of the present indications for BCG vaccination, arriving at the final conclusion that "The evidence now available argues strongly for the vaccinating of infants and children against tuberculosis in areas of high incidence and for those individuals who will be unavoidably exposed to tuberculosis (medical and nursing students, individuals in tuberculosis households, etc.), with revaccination at suitable intervals in order to maintain as high a level of immunity as possible."

At first glance, this might seem to constitute a rather sweeping recommendation and a radical depature from existing policy. This is, however, not necessarily the case, particularly in Canada. It must be admitted that, in the U.S.A., there are certain authorities in the field of public health in whose presence the letters "BCG" cannot be uttered with impunity. However, in

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Canada, there seems to be a greater degree of receptivity to the concept of expanded BCG vaccination, and the immunization of individuals who will be unavoidably exposed to tuberculosis has become routine practice throughout most of the country. The desirability of revaccination for maintenance of immunity has not as yet become a popular notion, but this situation appears to be the result of insufficient emphasis, and could be readily remedied. So far as the recommendations of the Committee are concerned, therefore, particularly as they apply to Canada, the only new suggestion is that vaccination be carried out in infants and children in areas of high incidence; and, in certain parts of Canada, notably the province of Quebec, the eastern seaboard, and certain segments of the Indian population, this is being done already, albeit on an experimental basis.

It would seem, therefore, that we in Canada are gradually becoming members of the "enlightened" group with respect to BCG vaccination; and there are those among us who would press for an even greater expansion of the indications for BCG vaccination in this country, to the point where such immunization be offered to all negative reactors to tuberculin, irrespective of their contact status. Let us, therefore, examine the arguments for and against such a policy.

The opponents of mass BCG vaccination argue that, in view of the current dramatic drop in tuberculosis mortality, such immunization is no longer needed. Such an argument, of course, loses sight of the fact that, although the mortality from tuberculosis has decreased precipitously in recent years, the morbidity from this disease has declined much more slowly. In fact, as the result of increasingly intensive case-finding efforts, there are, in some areas, more new cases of tuberculosis being discovered annually than was previously the case. Among unbiased observers of the situation, it is unhesitatingly conceded that tuberculosis is still a serious problem in many parts, if not all, of Canada; and this raises the question whether or not an effective vaccine would be of material aid in the control of tuberculosis morbidity in this country.

At first sight, one of the most potent arguments against BCG vaccination has been the presumed lack of safety of the procedure. In recent years, however, it has been virtually impossible to demonstrate conclusively that BCG has been the cause of serious injury or death in any individual to whom it has been administered. This has been strikingly demonstrated in a study in progress at Dalhousie University, in which thousands of BCG vaccinations have been performed by the multiple puncture method without a single serious untoward reaction. It should also be emphasized that, in Scandinavia, millions of vaccinations have been performed, and that, of this huge number, there were only four fatal outcomes, none of which could be unequivocally attributed to the vaccine. A further contention of the anti-vaccinationists is that BCG is not sufficiently standardized for present-day usage. It is generally agreed, however, that, with the advent of freeze-dried vaccine, it is now possible to standardize completely the viability, potency and sterility of BCG as well as to determine its safety before distribution. By this method of preservation, BCG vaccine can now be stored for periods up to four years with relatively little loss in its efficacy. In perfect fairness, however, one must take note of the fact that all biological products are subject to unexplained variations in potency, and that all batches should be tested along accepted lines before being released for use. As to the comparative safety of various immunization procedures, it may be added parenthetically that, in the case of smallpox vaccination, the extremely rare complication of post-vaccinal encephalitis has not prevented the widespread acceptance of this procedure.

Another suggestion repeatedly made by those opposed to mass BCG vaccination is that this procedure is not effective in the prevention of human tuberculosis. Such a statement fails to take note of the numerous valid studies demonstrating the efficacy of BCG vaccination that have been carried out during the past few years. Numerous references can be quoted of carefully conducted and controlled experiments, which should leave no doubt in the mind of an unbiased observer that BCG affords substantial protection against tuberculous disease; and, in this respect, studies carried out in this country by Ferguson occupy a front-rank position. Youmans[2] states that "If we accept the conclusion that BCG vaccine may effect an average of 80% reduction in the incidence of tuberculosis in vaccinated individuals over a four-year period, and that it practically eliminates tuberculous meningitis in the first years of life, BCG then becomes one of the most effective vaccines available for the protection of man against an infectious disease."

One of the more valid objections to mass BCG vaccination, stressed most strongly by specialists in public health and tuberculosis control, is that with such a program the usefulness of the tuberculin test might be lost to the epidemiologist. It is clear that, where the rate of tuberculous infection in the population is low, the detection of the small proportion of infected individuals by means of the tuberculin test is highly worth while; and there is an unmistakable trend during the past decade towards a numerical decrease in the tuberculin-sensitive portion of the population. However, if, as suggested by a recent British study,[3] BCG vaccination can result in an 80% reduction in the incidence of tuberculous disease in vaccinated individuals,

there is a strong probability that such a reduction might more than compensate for the lack of usefulness of the tuberculin test. This is therefore a matter that deserves the most careful and serious consideration.

Finally, since it is now considered acceptable practice to treat recent tuberculin converters with isoniazid, even in the absence of demonstrable tuberculous lesions, the question is sometimes asked, "Does not the availability of isoniazid chemoprophylaxis render BCG vaccination unnecessary?" This question loses sight of the fact that, in this connection, we are dealing with two different groups—on the one hand, patients with negative tuberculin status, and on the other, recent tuberculin converters. So-called chemoprophylaxis—that is, the administration of isoniazid to recent tuberculin converters—is therefore a procedure entirely divorced from the immunization of negative tuberculin reactors by BCG vaccination. If our conception of the immunology of tuberculosis is accurate, we have, in one case, patients recently infected with the tubercle bacillus, and in the other, individuals never infected. BCG vaccination is contraindicated for the former group and recommended for the latter. Conversely, in the tuberculin-converter so-called chemoprophylaxis (actually treatment of a cryptic infection) may be desirable, while there is clearly no point in administering an antimicrobial agent in the absence of infection.

From what has already been said, it can at least be concluded that there is as much evidence in favour of mass BCG vaccination as there is against such a policy. Under the circumstances, therefore, it would seem reasonable to suggest a thorough reconsideration of our present policies in this timely and urgent matter. Perhaps our own national tuberculosis association may deem it wise to give this subject intensive coverage at some future date. S.J.S.

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THE EPIDEMIOLOGICAL APPROACH TO MONGOLISM

An interesting contribution to the problem of mongolism has been made by Pleydell (*Lancet*, 1: 1314, 1957). Working in Northamptonshire, England, he observed that mongol children appeared to be born in groups in different areas at different times. During the 12-year period, 1944-55, a total of 84 mongols were born alive in the county and two were stillborn, giving an incidence of one mongol birth in every 613 live births and stillbirths. The incidence of such births varied considerably from month to month and year to year. The yearly incidence, for example, varied from one in every 1160 live births and stillbirths to one in 362. When the distribution of mongol births was related to locality it was found that whilst about a third could be regarded as isolated cases, the remaining two-thirds occurred in small groups. Thus of the 13 mongols born in 1947-48, no fewer than five were born in an area whose population was less than one-tenth of that of the county. Such findings led Pleydell to conclude that the unusual incidence in these cases was the result of an environmental factor which did not remain constant in any one locality, and he suggested that this factor might well be infection, more especially scarlet fever. From a study of the epidemiological patterns of notifiable infectious diseases over the 12-year period covered by the study, it appeared that scarlet fever had a closer association with the distribution of mongol births than had any other infection. The view was put forward that if the Northamptonshire findings were corroborated, they might well have repercussions in the field of prevention. Just as in the case of rubella, public health measures could be taken to prevent expectant mothers coming in contact with infection, or else immunization or chemotherapy could be started as soon as pregnancy was diagnosed in order to protect mother and fetus during the critical early months.

While paying due credit to the constructiveness of this approach it would nevertheless be premature to discount the possibility that agents other than infective might also play a decisive role in the causation of mongolism. This condition has been attributed in its time to many factors including advanced maternal age, uterine exhaustion, diminished viability of the ovum, fetal hyperthyroidism ceasing at birth, and congenital hypopituitarism. It has likewise been attributed to the simultaneous presence in the germ cell of five pairs of recessive factors or two dominant and four pairs of recessive factors carried in as many different chromosomes. Probably a fair body of opinion would subscribe to the view upheld by Penrose[1] that the causation of mongolism is a complex interaction between the mother and a fetus of specific genetic constitution. Whilst this specific constitution is believed to be common, it only occasionally results in mongolism. The additional factors required to produce a mongol defective seemingly range from maternal age to fetal anoxia. Ingalls[2] was inclined to stress the importance of the latter, which he associated with vaginal hæmorrhage during the first trimester of pregnancy, but he freely admitted a connection between mongolism and intercurrent infection during the same period. Further research along the lines indicated by Pleydell should undoubtedly prove

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helpful in arriving at a more informed opinion on the nature and significance of infection in this respect. ROBERT GIBSON

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THE ABUSE OF ANALGESICS

The fashionable and widely publicized agents of addiction on this continent include alcohol, heroin, barbiturates, analeptics and of course tobacco. Practically nothing is heard either in the medical or the popular press on the subject of the abuse of analgesic drugs, from which one would conclude that addiction to these agents is either rare or at least not dramatic. From the clinic of Professor Bleuler of Zurich, Switzerland, comes a reminder by Bernays[1] that in Switzerland at least these drugs do present a problem. In fact, says Bernays, the abuse of preparations containing a number of analgesics of the antipyretic group has reached such an extent there that it has become a topic of discussion among physicians. He records 22 cases of the chronic over-use of analgesic preparations, in which the patient voluntarily came to the clinic for treatment. He then notes that most of these persons had been using one or another of two popular pain killers, containing a pyrazolone derivative with phenacetin and caffeine or a similar compound with a barbiturate. The drugs had been taken in the first place to relieve pain, mostly headache or menstrual pain, and the daily dose was remarkably constant in many cases. Over a course of months or years of regular use, the dose had been raised until the average addict was consuming 10-30 tablets of his preparation daily.

Some patients were using other drugs of addiction and switching from one to another from time to time. Thus an occasional person would go through a period in which there was excessive consumption of alcohol or hypnotics and a decreased dosage of the analgesic. In some cases patients declared that in addition to relief of pain they were getting a stimulating or euphoric effect, which they failed entirely to get from ordinary aspirin preparations.

Patients tended to be irritable or explosive individuals with great lability of mood and often a bad family history. When signs of a psychosis were present, this was mainly of manic-depressive type. Physically, there was often a suggestion of infantilism or endocrine disturbances, and peptic ulcer was abnormally common. Signs of tetany or convulsive disorders were sometimes associated, but psychological testing revealed few abnormalities.

It is noteworthy that the strains and stresses of modern life appeared to play no part in this addiction; many patients were relatively inactive persons or rural dwellers.

The consequences of this long-continued consumption of abnormal quantities of analgesics were relatively mild. Five patients had some signs of renal damage, but anæmias or chronic urinary infection was rare. In no case was a granulocytopenia observed, in spite of the bad reputation of pyrazolone derivatives. However, a rather characteristic mental syndrome was present, including tiredness, anorexia, insomnia, loss of libido, and mild disturbances of gait and speech, combined with irritability and poor concentration. Episodes of acute psychosis resembling delirium tremens were occasionally observed.

The author advises in-patient treatment with immediate withdrawal of the drug, and finds that results of detailed individual psychotherapy are poor. Results of treatment are often disappointing; patients tend either to relapse or to take up some other addiction.

It has been suggested that these cases do not represent a true addiction; for example, withdrawal symptoms are by no means constant. Nevertheless, Bernays has no doubts on this point. He notes the association with other addictions in individual patients, and also the desire of the patient to be relieved of dependence on his favourite drug. Further study of this type of drug dependence should help to widen our knowledge of the addiction problem as a whole.

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CANADIAN JOURNAL OF SURGERY

The first issue of the new *Canadian Journal of Surgery* was published on October 1. It will appear quarterly and present to the world a balanced account of surgical activities in Canada.

The response to an appeal for pre-publication subscriptions was most gratifying, and many surgeons showed their faith in the new venture by sending in ten dollars before the journal had even appeared. Now that it is actually available, many more will doubtless wish to support this declaration of Canadian surgical independence. If you haven't already done so, send in your ten-dollar cheque now to *Canadian Journal of Surgery*, C.M.A. House, 150 St. George Street, Toronto 5, Ontario, and thus ensure that your subscription begins with the first issue. This issue contains contributions from almost all of the major surgical centres in Canada, carefully selected for you by your Editorial Board, as well as the first in a series of articles on the history of surgery in Canada. So start your subscription *now!*

Medical News in brief

POTENTIALITIES OF REHABILITATION

Yet another article has appeared showing that intensive attempts at rehabilitation of the chronic sick pay off handsomely. In the Homer G. Phillips Hospital, Washington, D.C., (*J. A. M. A.*, 164: 1633, 1957) a pilot rehabilitation study was set up in July 1953. This is a city-supported hospital for the care of indigents, and some 86 patients who were simply receiving custodial care because their treatment had reached a stationary level and who had every appearance of becoming permanently disabled were selected for rehabilitation. Their diagnoses were varied, cases including amputations, nerve injuries, hypertensive heart disease, chronic pancreatitis, paraplegia and hemiplegia, fractures, carcinomas and diabetes. Several patients had been living in the hospital for many years, and no attempt was made to select easy cases. Nevertheless at the end of three years 25 out of the 86 had returned to full employment and another 17 are on the way to complete rehabilitation. This means a probable return to active employment of about 50% of the series, and an additional 19 patients have been able to leave hospital for care at home.

In calculating the savings, the authors point out that 40 of these patients had already cost the community $483,000, much of which might have been saved. The rehabilitation service more than paid for itself.

TREATMENT OF PINWORM INFECTION

A report from Buffalo (*J. A. M. A.*, 164: 1651, 1957) fails to confirm the good results of treatment of pinworm infestation with a single oral bedtime dose of promethazine (Phenergan). Last year Avery reported a 97% cure rate in 100 patients so treated, but the Buffalo observers after treating 107 infected children with 125 mg. promethazine in a single oral dose obtained only a 5.3% cure rate, a rate even lower than the spontaneous one. It would seem that piperazine is still the treatment of choice.

RECTAL OR PROSTATIC CANCER?

Winter of Los Angeles (*Surg. Gynec. & Obst.*, 105: 136, 1957) draws attention to the fact that a carcinoma of the prostate with rectal manifestations may sometimes be confused with a carcinoma of the rectum. No less than 11% of a group of 225 patients with carcinoma of the prostate had such rectal involvement as to create a differential diagnostic problem. For differential diagnosis, they suggest first taking a biopsy of the lesion by punch, open surgery or transurethral resection, supplementing this with estimation of serum acid phosphatase, particularly the "prostatic portion". The finding of malignant cells in the prostatic secretion, positive Gömöri stains of biopsy tissue or elevated acid phosphatase assays of the latter may lend support to the clinical diagnosis of prostatic cancer. In addition, radiographs of the pelvis and vertebræ for metastases, and barium studies of the gastro-intestinal tract, are valuable. Cystourethrography and cystoscopy may reveal significant findings in the bladder or prostatic ureter. Finally, if the diagnosis is still uncertain, a short course of œstrogen therapy may resolve the problem by its favourable effect on a prostatic lesion.

OSTEOGENIC SARCOMA

After a follow-up study of 430 patients who had pathologically verified osteogenic sarcoma and were treated at the Mayo Clinic between 1909 and 1955, Coventry and Dahlin (*J. Bone & Joint Surg.*, 39A: 741, 1957) report a five-year survival rate considerably above that to be found in the literature. Of the entire group of patients with osteogenic sarcoma, almost 20% survived for five years and 15.3% for ten years after the date of definitive treatment. These rates were somewhat bettered for patients with lesions readily amenable to amputations. The five-year survival rate for patients with lesions of the tibia was 34.6%. The usual treatment in this series was amputation, and the authors see no reason to prefer any other type of treatment unless amputation is impossible. They adopt the general principle of amputating through the bone above the one affected by tumour, except in the case of sarcoma of the distal part of the femur, for which amputation has sometimes been performed through the upper part of the femur.

CLASSIFICATION OF LUNG CANCER

At an all-Russian conference on problems of lung cancer, Professor Savitsky of Moscow suggested a classification of bronchogenic carcinoma primarily into central and peripheral types. The central forms include (a) endobronchial carcinoma; (b) the peribronchial nodular type; (c) ramifying type. Peripheral forms include (a) spherical tumour; (b) pneumonia-like form; (c) carcinoma of the lung apex. Atypical clinical forms which do not fit into this classification include (a) mediastinal; (b) osseous; (c) cerebral; (d) hepatic; (e) gastro-intestinal; (f) cardiovascular forms. About 80% of patients suffer from the central type. In Moscow 65% of central carcinomata affect the upper lobes and give rise to early clinical symptoms due to growth of the tumour into the lumen of a large bronchus with atelectasis and obstructive pneumonia as complications. With peripheral types there is a long latent period ending with the same type of clinical picture.—A. I. SAVITSKY, *Khirurgia*, No. 5: 10, 1957.

(Continued on advertising page 57)

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MEDICAL FILMS

CONTINUING the listing of available films on medical and related subjects, we list below additional films in the field of anæsthesiology. These films are held in the National Medical and Biological Film Library and are distributed by the Canadian Film Institute, 142 Sparks Street, Ottawa, Ontario. Evaluations, where given, are those submitted by the distributor.

Operative Shock (1945) Sound B & W 16 minutes

Produced by Realist Film Unit, for Imperial Chemical Industries Limited. Technical Advisers: Department of Anæsthetics, Westminster Hospital, London, England. *The Technique of Anæsthesia series, No. 10.*

Description.—This instructional-training film illustrates the causes, signs, preventive measures and treatment of shock arising during a surgical operation. Signs of operative shock, and point on pulse and b.p. chart at which these clinical signs appear. The following causes of shock, and preventive measures in each case, are discussed: dehydration and heat loss; minor accidents of anæsthesia; surgical stimuli; prolonged deep anæsthesia; prolonged suboxygenation; sudden changes in posture; low blood pressure; hæmorrhage. Treatment: use of intravenous drip saline given from start; cases where treatment immediately necessary; cases where permissible to watch patient for spontaneous recovery; use of blood substitutes and whole blood; lowering head of table; ensuring a clear airway; oxygen and lightening anæsthesia to safe level; when to stop operation for administration of intravenous drip; when to request surgeon to finish operation as quickly as possible to save patient's life; responsibility of anæsthetist to supervise postoperative recovery from shock.

Appraisal (1946).—An excellent film for teaching purposes. We do not agree with every detail of theory expounded, or of therapeutic measures adopted, but heartily recommend the film for medical students in the clinical years, interns, general practitioners and specialists in anæsthesia. *Unsuitable for non-medical audiences.*

Availability.—National Medical and Biological Film Library ($1.50). Purchase (in Canada) from Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, P.Q.

Nitrous Oxide-Oxygen-Ether Anæsthesia (1944) Sound B & W 26 minutes.

Produced by Realist Film Unit, for Imperial Chemical Industries Limited. Technical Advisers: Department of Anæsthetics, Westminster Hospital, London, England. *The Technique of Anæsthesia series, No. 3.*

Description.—An instructional-training film, demonstrating the principles and practice of continuous flow nitrous oxide-oxygen-ether anæsthesia. Construction and operation of an English-type gas machine are shown and explained by animation. The general principles of continuous flow anæsthesia are outlined and the film then demonstrates techniques and practice as follows: preparation of apparatus; preparation and examination of patient; induction to various stages, noting possible complications; maintenance, noting function of rebreathing bag, procedure in cases requiring additional oxygen, and procedure for maintenance of same depth when tissues become saturated.

Appraisal (1945).—While the type of apparatus used is never seen in Canada, the demonstration of underlying principles is so good that this film is unhesitatingly recommended for senior medical students, general practitioners, interns, nurses and specialists in anæsthesia. Animation is especially good; photography and diction are excellent. As title suggests, film is not a complete exposition of modern nitrous oxide-oxygen anæsthesia. *Unsuitable for non-medical audiences.*

Availability.—National Medical and Biological Film Library ($2.50). Purchase (in Canada) from Distribution Branch, National Film Board, P.O. Box 6100, Montreal 3, P.Q.

Spinal Anæsthesia (1944) Sound B & W 34 minutes.

Produced by Realist Film Unit, for Imperial Chemical Industries Limited. Technical advisers: Department of Anæsthetics, Westminster Hospital, London. *The Technique of Anæsthesia series, No. 8.*

Description.—An instructional-training film, illustrating the general principles and practice of spinal anæsthesia with light and heavy Nupercaine. Lumbar puncture is described and illustrated, with the aid of animation, in both lateral and sitting positions and in cases of scoliosis and lordosis. Preparation of apparatus, and difficulties and corrective procedures, are discussed. Demonstration of the course of hyperbaric and hypobaric solutions, using a curved glass tube to represent the spinal canal. Technique of administration shown for: low spinals to third sacral nerve and to first lumbar nerve with slight barbotage; mid spinals to tenth dorsal nerve, with more barbotage; high spinal to fifth dorsal nerve. Technique of lumbar puncture and administration for unilateral anæsthesia. Supplementary anæsthesia with nitrous oxide or intravenous pentothal. Risks of spinal anæsthesia; precautions.

Appraisal (1946).—An excellent film which tells clearly the general principles of spinal anæsthesia, but illustrates only one method using one particular drug. Animation and diagrams very good. Recommended for senior medical students, interns, general practitioners and specialists in anæsthesia. *Unsuitable for non-medical audiences.*

Availability.—National Medical and Biological Film Library ($3.00). Purchase (in Canada) from Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, P.Q.

The Signs and Stages of Anæsthesia (1945) Sound B & W 23 minutes.

Produced by Realist Film Unit, for Imperial Chemical Industries Limited. Technical Advisers: Department of Anæsthetics, Westminster Hospital, London. *The Technique of Anæsthesia series, No. 1.*

Description.—An instructional-training film, illustrating the signs and stages of inhalation anæsthesia, using ether as an example. The four stages of anæsthesia are described and illustrated diagrammatically, using the Guedel classification. Reflex signs connected with respiration are shown schematically on the diagram, illustrating the character of respiration through the first and second stages, the four planes of the third stage, and the fourth stage. Laryngeal reflex, salivation and mucus production, and vomiting reflex are similarly described and illustrated. All these reflexes are then shown in an anæsthetized patient through the four stages. Using both clinical illustrations and the schematic diagram, the various eye reflexes are described in detail through the four stages; effect of premedication on eye reflexes is shown.

Appraisal (1946).—The film is heartily approved and emphatically endorsed. It is the best yet produced showing the signs and stages of anæsthesia and is widely recommended for use as a teaching aid for medical students and postgraduate students in the specialty of anæsthesia. *Unsuitable for non-medical audiences.*

Availability.—National Medical and Biological Film Library ($2.00). Purchase (in Canada) from Distribution Branch, National Film Board of Canada, P.O. Box 6100, Montreal 3, P.Q.

(To be continued in our next issue)

REVIEW ARTICLE

HÆMOLYTIC DISEASE OF THE NEWBORN DUE TO Rh ISOIMMUNIZATION*

A TEN-YEAR REVIEW WITH EMPHASIS ON EXCHANGE TRANSFUSION

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ERYTHROBLASTOSIS due to Rh incompatibility presents two basic problems in management, the antepartum inhibition of the hæmolytic process with maintenance of a viable fetus and treatment of the baby in the newborn period with prevention of kernicterus and death.

At present, there is no effective treatment of the isoimmunization process in the antenatal period. During the past decade, exchange transfusion has been established as a most important and useful form of neonatal treatment. It has decreased the incidence of kernicterus and has reduced neonatal mortality.[2, 3, 5, 6, 10-13]

The present survey was undertaken because it was thought that a detailed review of both clinical and laboratory features of exchange transfusion therapy over a ten-year period at the Royal Victoria Montreal Maternity Hospital would be of interest.

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†First Prize Award, Montreal Obstetrical and Gynæcological Society Essay Competition, 1957.

METHODS AND MATERIALS

The clinical observations and laboratory data were obtained from the records of the Royal Victoria Montreal Maternity Hospital. Hæmoglobin levels[7] and total serum bilirubin levels[8] were obtained from heel puncture blood. Serum antibody titrations in albumin were performed using Rh positive cells according to the method of Diamond and Denton.[4] The antibody levels listed in "Results" refer entirely to albumin antibody titres. Saline antibodies were not estimated serially because they are not as important in the assessment of the disease. A direct Coombs test was performed in all cases.

RESULTS

Major emphasis has been placed on the results of the five years from 1951 to 1955, since this period was associated with a more intensive investigation of cases of hæmolytic disease of the newborn, as well as with a greater degree of uniformity in management by a number of different pædiatricians. Hence, it will be presented first. The period 1946 to 1950 has been reviewed so as to emphasize certain aspects of these results.

TABLE I.

Year	*No. of E. fetalis / total deliveries*	*Incidence*	*No. treated with exchange transfusion*	*% exchange transfusion in all cases*	*% exchange transfusion in all live-born babies*	*No. live-born babies not given exchange transfusion*
1951	12 / (3132)	1 / 261	5	41.6%	45.4%	5
1952	21 / (3392)	1 / 161	9	43%	47.3%	5
1953	32 / (3317)	1 / 107	20	67.7%	70%	8
1954	18 / (3451)	1 / 191	12	66.7%	92.3%	1
1955	27 / (3329)	1 / 123	20	74.1%	87%	1
Total	110 / (16,621)		66			20
Average		1 / 151		60%	68.4%	

1. THE PERIOD 1951-1955

A. *Incidence.*

There were 110 cases of hæmolytic disease of the newborn due to Rh incompatibility during this period (Table I). Sixty-six (60%) received exchange transfusion.

The percentage of cases given exchange transfusions increased progressively, with the lowest value in 1951 (41.6%), and the highest value in 1955 (74.1%). The over-all incidence of hæmolytic disease of the newborn (Table I)

TABLE II.

Year	Total cases E. fetalis	Total perinatal mortality %	Total deaths			Deaths in 66 babies treated with exchange transfusion
			Ante-partum	Intra-partum	Post-partum	
1951	12	2 (16.7%)	1	0	1	1
1952	21	7 (33.3%)	2	0	5	3
1953	32	4 (12.5%)	1	2	1	0
1954	18	5 (27.7%)	4	1	0	0
1955	27	6 (22.2%)	4	0	2	1
Total	110	24	12	3	9	5 (7.5%)
Average		(21.8%)				

ranged from 1 in 107 to 1 in 261, and averaged 1 in 151 for the entire five-year period.

There were 24 cases of fetal and neonatal deaths and 20 live babies among the 44 infants who did not receive exchange transfusions (Table I). Eighteen of the 20 live-born infants were delivered between 1951 and 1953. In 1954 and 1955 almost all babies born alive received exchange transfusions. The percentage of exchange transfusions in all live-born affected babies increased from 45.4% in 1951 to 87% in 1955.

As shown in Table II, perinatal mortality ranged from a low of 12.5% (four cases) in 1953 to a high of 33.3% (seven cases) in 1952. The average perinatal mortality for the entire five-year period was 21.8% (24 cases). It is impossible to relate perinatal mortality to the frequency of administration of replacement transfusions (Tables I and II). When the perinatal mortality was divided into antepartum, intrapartum and postpartum periods, pertinent data were obtained. Twelve deaths occurred ante partum, three intra partum and nine post partum.

Five (7.5%) of the 66 babies treated by exchange transfusion died during the postpartum period. Four of the 20 live-born babies not treated with exchange transfusion died post partum. Seven of the nine postpartum deaths occurred from 1951 to 1953. Eight of the 12 antepartum deaths occurred in 1954 and 1955. Hence, during 1954 and 1955 the more dangerous period for the baby was before delivery, while from 1951 to 1953 the more dangerous period was after delivery. The number of cases involved do not permit a definite statement regarding the significance of this observation.

B. *Administration of Exchange Transfusions.*

1. Exchange transfusions were administered via the umbilical vein in 65 infants and in only one instance via the saphenous vein. The volume of blood administered ranged from 100 c.c. to 500 c.c. and averaged 357 c.c. This average value is equivalent to 50 c.c. of blood per lb. of body weight. In three cases of postpartum deaths the amounts of blood given were limited by the poor condition of the babies and ranged from 135 c.c. to 152 c.c.

TABLE III.

Year	No. of cases receiving exchange transfusions				Total No. exchange transfusions per year
	One transfusion	Two transfusions	Three transfusions	Four transfusions	
1951	5	0	0	0	5
1952	7	1	1	0	12
1953	20	0	0	0	20
1954	6	5	0	1	20
1955	12	6	0	2	32
Total	50	12	1	3	89

Single exchange transfusions were given to 50 babies (Table III). Multiple exchange transfusions were given to the remainder as follows: Twelve patients received two exchange transfusions, one patient received three, and three patients received four transfusions. Thus, there was a total of 89 exchange transfusions in 66 babies. The annual number increased progressively from five in 1951 to 32 in 1955.

TABLE IV.

No. of cases	Time of administration of first exchange transfusion after birth	No. of neonatal deaths
44	3 hrs.	4
12	6 "	0
2	12 "	1
3	24 "	0
3	48 "	0
2	More than 48 "	0

2. *The time of administration* of each exchange transfusion was divided into six periods (Table IV). Forty-four exchange transfusions were given within three hours of birth, 12 within six hours, three within 12 hours, seven within 24 hours, nine within 48 hours and 14 were administered more than 48 hours after birth.

The first exchange transfusion was started within the first six hours of life in 84.8% of cases (Table IV). It is of interest that four of the five babies dying post partum were first transfused within three hours of birth.

TABLE V.

Number	*Immune antibody titre*	*Neonatal death*
1	0	0
4	1	0
5	2	0
5	4	0
10	8	0
12	16	1
19	32	3
7	64	1
1	128	0
1	1024	0

C. *Immune Antibody Titres.*

A wide range (0 to 1024) of immune albumin antibody titres was recorded ante partum (Table V). In 56 cases the titre listed is the highest recorded after a progressive rise. Only 10 cases did not have a rising titre. Forty-nine cases were in the 8 to 64 range of titre (Table V). Fourteen of the 16 babies who were given multiple exchange transfusions were also in this narrow antibody titre range. A titre of 32, present in 19 cases, was associated with the largest single group of multiple exchange transfusions (seven cases), and with three of the five postpartum deaths.

averaged 3195 g. Table VI shows that a greater proportion of premature infants than mature infants died in the neonatal period and required multiple exchange transfusions. Two premature deaths were in babies delivered by Cæsarean section because of probable hæmolytic disease of the newborn. The average length of hospitalization of the premature infants was 23.8 days as compared with 12.3 days for the mature infants. This difference may have been due solely to prematurity.

TABLE VII.

Gestation age (weeks)	*No.*	*Neonatal deaths*	*No. given multiple exchange transfusion*	*No. of premature babies*	*Range of immune antibody titre*
33	1	0	1	1	16
36	5	0	3	3	2-32
37	7	0	0	1	4-128
38	14	3	2	2	1-1024
39	7	1	1	0	1-32
40	24	1	7	2	0-64
41	6	0	0	0	8-32
42	2	0	2	0	16-64

Eight of the nine premature babies (Table VII) were born at 36 to 40 weeks of gestation and only one baby was born before the 36th week.

TABLE VI.

Baby	*No.*	*No. given multiple exchange transfusions*	*No. given supplementary simple transfusions*	*No. neonatal deaths*	*Birth weight (grams)* *Range*	*Average*
Mature	57	12	20	3	2530 - 4120	3195
Premature	9	4	2	2	1753 - 2500	2201

D. *Multiple Exchange Transfusions.*

As shown in Table VI, 12 mature and four premature babies were given multiple exchange transfusions.

E. *Supplementary Simple Blood Transfusions.*

A total of 22 babies were given supplementary simple transfusions of 30-80 c.c. of whole blood or packed cells (Table VI). Sixteen babies received one such transfusion, five babies received two transfusions and one baby received three transfusions. The numbers of supplementary simple transfusions given were not related to the time of administration of the initial exchange transfusion, the numbers of exchange transfusions given to each baby or to prematurity.

F. *Prematurity.*

Of the 36 babies receiving exchange transfusions nine were premature infants. Their birth weight ranged from 1753 to 2500 grams, and averaged 2201 g. The birth weight of the mature babies ranged from 2530 to 4120 g., and

There was no relationship between prematurity and the antepartum antibody titre (Table VII), which ranged from 0 to 1024.

G. *Effect of Exchange Transfusion on Hæmoglobin Level.*

The cord hæmoglobin value at birth was determined in 63 of the 66 babies treated with exchange transfusions. It was less than 15.6 g. % in 47 babies, ranging from 4 to 15.6 g. % and averaging 11.7 g. %. In 16 cases it was greater than 15.6 g. %, ranging from 16.2 to 22.8 g. % and averaging 17.9%. At discharge the heel hæmoglobin values ranged from 7.0 to 17.0 g. % and averaged 12.0 g. % (Table VIII).

TABLE VIII.

	Cord hæmoglobin at birth *<15.6 g.%*	*>15.6 g.%*	*Heel hæmoglobin at discharge*
Number	47	16	57
Range	4-15.6 g.%	16.2-22.8 g.%	7.0-17.0 g.%
Average	11.7 g.%	17.9 g.%	12.0 g.%

The hæmoglobin level at the time of discharge was less than at birth in 43 babies and was more than at birth in 11 babies. In one case the same values were obtained and in two cases there was no initial hæmoglobin value available for comparison purposes. In general, then, there was a definite trend to increased anæmia at the time of discharge, regardless of the birth hæmoglobin levels.

This is further emphasized by the following observations in 10 of the 11 cases where the discharge hæmoglobin was greater than the initial values: Four of these cases had been given supplementary transfusions, three were given both supplementary and multiple exchange transfusions, and three were given only multiple exchange transfusions. Thus, it is possible that artificial elevation of the hæmoglobin may have taken place in these 10 cases.

H. *Serum Bilirubin.*

Total serum bilirubin values were recorded repeatedly in each of 41 cases. The maximal neonatal level ranged from 1.6 mg. % to 28.4 mg. %, with an average of 14.9 mg. %. This maximum value followed a progressive rise in the bilirubin level.

In 26 of these 41 cases, a variable degree of anæmia was present at birth. A comparison between the hæmoglobin at birth and subsequent levels of serum bilirubin is presented in Table IX. Anæmia was present at birth in all

TABLE IX.

Serum bilirubin Range (mg.%)	*No.*	*Hæmoglobin at birth 12.0-15.6 g.%*	*Less than 12 g.%*
10 - 15	9	7	2
15 - 20	12	10	2
>20	5	2	3

infants whose serum bilirubin reached 10 mg. %. The severest anæmias seemed to be in those infants whose bilirubin rose to over 20 mg. %, but the series is too small to definitely relate the severity of anæmia to the amount of hyperbilirubinæmia.

I. *Direct Coombs Test Following Exchange Transfusion.*

Every baby in this series had a positive direct Coombs test at birth, before treatment with exchange transfusion. The Coombs test was recorded in 24 cases after exchange transfusion, and in 12 cases it had become negative before the babies' discharge from hospital.

J. *Clinical Observations.*

Hepatomegaly, œdema and central nervous system changes were assessed and were correlated with anæmia and hyperbilirubinæmia.

TABLE X.

Hepatomegaly Degree in fingers' breadths	*No.*	*Associated œdema*	*Neonatal death*
0	28	0	0
1FB	6	1	0
2FB	17	2	2
3FB	6	2	0
4FB	1	0	0
5FB	7	4	3
6FB	1	0	0
Total.....	66	9	5

The degree of hepatomegaly ranged from no enlargement to 6 fingers' breadths below the right costal margin (Table X). In a total of 51 cases, the liver was within the normal range of 0 to 2 fingers' breadths. There was definite hepatomegaly in 15 cases. Three of the five postpartum deaths were in this latter group.

Œdema of mild degree was noted at birth in nine babies (Table X). Hepatomegaly was present in six of these babies.

There were detectable central nervous system changes at birth in six babies (Table XI). These changes consisted of respiratory depression, hypotonicity or hypertonicity. Four of these babies had associated hepatomegaly and five were known to be anæmic at birth. In the two cases in which serum bilirubin was obtained, a maximum level above 10 mg. % was recorded. There were only two babies with even a suggestion of kernicterus at the time of discharge.

The major clinical observations in the five infants who died post partum were as follows: One baby had only hepatomegaly. Four babies had both hepatomegaly and œdema. Three of the five babies had hepatomegaly, œdema and central nervous system changes. The hæmoglobin value at birth was known in four babies and ranged from 8.7 to 13.9 g. %.

TABLE XI.

Changes at birth in six babies	*Anæmia at birth*	*Hyperbilirubinæmia*	*Hepatomegaly*	*Possible kernicterus*	*Neonatal death*
			Fingers' breadths		
Decreased muscle tone	+	+	3	0	No
Respiratory and muscle tone depression	+	+	5	0	+
Hypertonicity	+	No	3	?	No
Respiratory depression	?	No	5	0	+
Respiratory depression	+	No	2	0	+
Respiratory depression	+	No	2	?	No

K. *Management of Labour.*

There were 57 vaginal deliveries and nine Cæsarean sections. Seven Cæsarean sections were performed because of previous erythroblastosis fetalis. Two of these seven babies were premature infants and died. Cephalo-pelvic disproportion was the indication for the remaining two Cæsarean sections. Medical induction was instituted successfully in three cases.

2. THE PERIOD 1946 TO 1950

In this five-year period the incidence of diagnosed cases of erythroblastosis fetalis was 1 in 262. There were 15 antepartum deaths (23.4%) and 21 neonatal deaths (32.8%), with a total perinatal mortality of 36 cases (56.2%) out of a total of 64 cases (Table XII).

TABLE XII.

	1946 - 1950		*1951 - 1955*	
	No.	*%*	*No.*	*%*
Antepartum and intrapartum deaths....	15	23.4	15	13.6
Postpartum deaths.....	21	32.8	9	8.2
Perinatal mortality.....	36	56.2	24	21.8
Live babies.....	28	43.8	66	78.2

The treatment of these infants during 1946 to 1950 is listed in Table XIII. Among the 49 babies who were born alive, 13 did not receive blood transfusions of any kind and nine died, and 23 babies were given simple blood transfusions and seven died. The remaining 13 babies were given exchange transfusions and five died. Exchange transfusions were not administered before 1948.

TABLE XIII.

Treatment of babies 1946 - 1950	*No.*	*Total postpartum deaths*	*Postpartum deaths in the 8 live-born premature infants*
No blood transfusion.....	13	9	2
Simple blood transfusion..	23	7	3
Exchange transfusion....	13	5	3

Twenty of the 64 babies during 1946 to 1950 were premature. Twelve of the premature babies died before birth and the remaining eight died in the neonatal period. Three of the latter infants were given exchange transfusions, three were given simple blood transfusions and two infants did not receive either form of transfusion (Table XIII).

3. BABIES NOT TREATED BY EXCHANGE TRANSFUSION—1951-1955

During this period 20 babies (18.2%) were not treated by exchange transfusion. Laboratory data were available in only 13 of the cases. In general, the disease in these infants was of a milder nature than in those treated by exchange transfusion. For example, the average hæmoglobin level at birth was higher by 2 g. %, and the hospitalization was 1.8 days shorter. At discharge the average hæmoglobin was 3.2 g. % higher. There were no cases with œdema or central nervous system changes during the neonatal period.

Ten of the 13 babies did not receive any special treatment. The remaining three were given simple blood transfusions, but in two of these cases there had been an unsuccessful attempt at exchange transfusion. The condition in these two cases was not as mild as in the others and successful exchange transfusion would have been a better treatment.

DISCUSSION

A. *Comparison of the 1946-1950 period with that of 1951-1955.*

It is apparent from the foregoing results that the treatment of hæmolytic disease of the newborn at the Royal Victoria Montreal Maternity Hospital has improved basically during the ten years from 1946 to 1955. The usefulness of exchange transfusion became apparent during the latter portion of 1946-1950 and it has become the mainstay of treatment in this disease.

A comparison of the results in the two five-year periods illustrates the value of exchange transfusion in reducing fetal wastage. The perinatal mortality was decreased from 56.2% during 1946-1950 to 21.8% during 1951-1955. This was due to a reduction in both antepartum and postpartum deaths (Table XII), with particular emphasis on the latter category. The improvement in the death rate is likewise reflected in the salvage of premature infants. Seven of nine premature infants survived during 1951 to 1955, whereas each of the live-born premature infants in 1946 to 1950 perished.

It is possible, however, that the aforementioned improvement may have also been due to a fundamental change in the hæmolytic disease with a diminution in its severity during the period extending from 1951 to 1955. This is suggested by the observation that the proportion of antepartum deaths was less during this five-year period (13.6% versus 23.4%), even though the antepartum management was subsequently the same as in the previous five-year period. Confirmation of this impression must await reporting of data from other centres.

The greater salvage of premature infants during the period 1951 to 1955 may be due, in part, to such a fundamental change. In the case of premature infants, part of this salvage must also be attributed to the improvement in nursing techniques which took place between 1951 and 1955. The major factor, however, was undoubtedly the institution of exchange transfusion therapy.

B. *1951-1955.*

During this period, there was a progressive increase in the use of exchange transfusions as the treatment of choice for hæmolytic disease of the newborn. Increasing willingness to give multiple exchange transfusions to selected cases followed upon greater familiarity with the technique. This has been associated with a decreased incidence of neonatal death, notable in 1954-1955 (Table II).

The perinatal mortality (21.8%) for the entire five-year period includes a higher proportion of antepartum deaths during 1954 and 1955. These data emphasize the absence of control of the erythroblastotic process in the antepartum period, which remains the period of greatest danger to the baby. Our perinatal mortality statistics are similar to the 22.1% of Teate[11] and the 20% of Allen *et al.*[3]

Value of Timing of Exchange Transfusions:

In 56 cases (84.8%), the first exchange transfusion was administered within six hours of birth and five of these babies died. In the remaining 10 cases the disease was mild and the later administration of exchange transfusion did not have deleterious effects. Although early exchange transfusion is desirable, it is apparent that this procedure may not prevent death if the disease is sufficiently severe.

Additional Transfusion Therapy:

Multiple exchange transfusions and supplementary simple transfusions are comparable only because they are both given in the neonatal period. Multiple exchange transfusions have the primary purpose of treatment of a persisting hæmolytic process, as indicated by a recurrent rise in total serum bilirubin, often with an associated decline in the hæmoglobin level. In one-third of the series (22 cases), treatment with exchange transfusion, either single or multiple, required supplementation by simple transfusion of whole blood or packed cells to combat anæmia not associated with a rising serum bilirubin. It is possible that the numbers of single transfusions might have been reduced by employing packed red cells more liberally in the replacement transfusions.

It is noteworthy that multiple exchange transfusions did not cause any physical harm to the babies. Repeated use of the umbilical vein presented no difficulty.

Influence of Exchange Transfusion on Hæmoglobin Levels:

After replacement transfusions the neonatal hæmoglobin values tend to decrease. This is probably due to a number of factors, including some continuation of hæmolysis. Approximately one-quarter of the fluid administered in replacement transfusions was a citrate-dextrose diluent; this may have resulted in inadequate replacement and hence may have contributed to the anæmia. From the clinical point of view it is questionable whether this depressant effect on the hæmoglobin level is of importance, particularly if this level is not less than 12 g. %. However, only further studies, including follow-up during the first year of life, can result in a definitive opinion about this matter. In 10 cases where the hæmoglobin value was greater at the time of discharge than at birth there was a background of artificial supplementation by means of multiple exchange transfusions or simple blood transfusions.

Prematurity:

Neonatal deaths and administration of exchange transfusion were relatively more frequent in the nine premature infants than in the mature babies. A number of authors[1, 6, 9, 10] have commented upon the higher mortality rate of hæmolytic disease of the newborn in premature infants. It would seem then that premature infants are less able to withstand the effects of the hæmolytic disease than the mature ones.

This review indicates the inadequacy of gestation age as a criterion of prematurity. Eight of the nine premature infants were born between 36 and 40 weeks of gestation—that is, during the period when one would expect the baby to be mature.

Immune Antibody Titres:

The specific level of the immune antibody titre cannot be used as an accurate index of the severity of the hæmolytic disease. Thus, the most severely affected babies in this series were in a moderate range of titre (16 to 64) and there was no relationship between antibody titre and the need for multiple exchange transfusions.

A progressive antepartum rise in the titre is probably a much more important criterion for prognosis and management than is the specific value of the titre—especially when the latter is less than 128.[1, 11, 14] It must be realized when interpreting antepartum titres that they reflect a state of affairs in the mother, and give only a broad indication of events taking place in the baby.

Clinical Observations:

The various combinations of hepatomegaly, œdema, central nervous system changes and anæmia indicate that a severe degree of hæmolytic disease may be present without causing perinatal death. In some of these cases treatment with exchange transfusion was sufficient to keep the baby alive and to prevent further physical deterioration. In only two babies was there a suggestion of kernicterus at the time of discharge.

Five of the nine postpartum deaths were in the group showing the above clinical findings. Hence, there is a degree of severity of the hæmolytic disease which creates damage that cannot be reversed by one or more exchange transfusions.

Exchange transfusion is the only means currently available for removing serum bilirubin, immune antibodies and sensitized red cells from the blood (in 12 of 24 babies, the direct Coombs test became negative before discharge from hospital). It is a relatively simple and innocuous procedure and is usually well tolerated by the baby, provided that he is not already too severely stricken by the disease. Nevertheless, one must be cognizant of occasional complications such as thrombocytopenia, heart failure and ruptured spleen.

Termination of Pregnancy:

Only 13 babies were delivered before the 38th week of gestation. Seven pre-term Cæsarean sections in 66 cases does not constitute a major swing to early delivery in hæmolytic disease of the newborn, although it is about twice the over-all incidence for Cæsarean sections. There was no significant use of medical inductions for the early termination of pregnancy. In two cases early delivery by Cæsarean section did not ensure the babies' survival. Our own results and those of others[1, 3, 6, 10, 11] indicate that early delivery of erythroblastotic infants is not indicated routinely because of the dangers of prematurity.

Allen *et al.*[3] and Jacobs and Kohn[9] suggest that pre-term delivery is still the only way to prevent continued damage to the baby. This method of management may be considered in cases where there has been a history of previous death due to hæmolytic disease of the newborn, but even in these cases, because of the difficulty of correlating prematurity with gestation age, one should attempt to ascertain the maturity of the fetus—for example, by x-ray visualization of a femoral epiphyseal centre. A mature infant at 36 weeks of gestation has a better prognosis than a premature baby at 38 weeks.

C. *Babies not Treated by Exchange Transfusion in the 1951-1955 Period:*

The percentage of cases which did not receive such treatment (18.2%) compares with the incidence of 10-20% quoted by Diamond *et al.*[5] This group of cases is too small for a comparison with the much larger group who received exchange transfusions. One may infer that not all cases of hæmolytic disease of the newborn are of sufficient severity to warrant administration of exchange transfusion, but they constitute a definite minority and are not easily diagnosed. Treatment might be deferred if the serum bilirubin does not rise above 10 mg. % and if the hæmoglobin value is not less than 15 g. %.

The major objective in postpartum management is to prevent kernicterus or death of the baby, and because of the difficulty of early assessment of the severity of the disease it may be wiser to treat all babies with exchange transfusion, preferably within six hours of birth. This is emphasized by the fate of one of the two infants who received simple blood transfusion after an unsuccessful attempt at administration of an exchange transfusion. This baby died at 2 years, with cerebral palsy and kernicterus.

SUMMARY AND CONCLUSIONS

1. Findings are reviewed in 110 cases of hæmolytic disease of the newborn admitted to the Royal Victoria Hospital during 1951-1955 and 64 cases admitted during 1946-1950. During 1951-1955, 66 babies received a total of 89 exchange transfusions and this measure significantly improved the neonatal mortality. Consequently, early replacement transfusion has become the treatment of choice at the Royal Victoria Hospital.

2. The clinical and hæmatological features of the disease are reviewed. Anæmia, often present at birth, could not be correlated with the degree of subsequent hyperbilirubinæmia. Premature infants with the disease did not fare as well as mature infants. An increasing hyperbilirubinæmia was the most important single criterion for multiple exchange transfusions.

3. Exchange transfusion had certain limitations. A mortality of 7.5% in treated cases indicated that in severely affected babies the disease may be irreversible. Treatment with exchange transfusions was often followed by increased anæmia, and one-third of the babies so treated required supplementary simple blood transfusions.

4. Although recent advances in postpartum management of hæmolytic disease of the newborn have been substantial, the primary problem of antepartum therapy remains unsolved.

We wish to acknowledge and express our appreciation to the following for their participation in the study and care of the patients: Dr. Newell W. Philpott, Emeritus Professor of Obstetrics and Gynæcology; Dr. George B. Maughan, Professor of Obstetrics and Gynæcology; Dr. Jessie Boyd Scriver and Dr. Aubrey K. Geddes, Pædiatricians-in-Charge; Dr. Paul Weil, Director of the Blood Transfusion Service, and the members of the Pædiatrics, Obstetrical and Blood Transfusion Services of the Royal Victoria Hospital; Dr. Lorne Shapiro and the staff of the Bessborough Laboratory of the Royal Victoria Hospital.

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GENERAL PRACTICE

HÆMOLYTIC DISEASE*

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ONE OF THE COMMONEST and sometimes most puzzling problems encountered by the physician is a patient with an anæmia of which the cause is obscure. Deficiency, marrow depression and blood loss are readily brought to mind as etiological possibilities, but there has been a tendency in the past to neglect consideration of hæmolytic processes as a cause of anæmia. There are several reasons for this. Until fairly recently the etiology and pathogenesis of many of these anæmias was quite obscure, and treatment was consequently not very specific. In addition, their clinical manifestations often tend to be quite subtle and difficult to detect. In the past few years, however, such strides have been made in techniques of diagnosis and treatment that now one can say that a working knowledge of the various factors producing premature destruction of the erythrocyte is not only theoretically interesting but is of great practical importance.

The normal human erythrocyte remains intact in the circulating blood for about 120 days. If, however, the cell is defectively formed, or is subjected to abnormal disruptive influences in its environment, it disintegrates sooner, and a hæmolytic process is said to be present. Thus it may be said that there are two general mechanisms of hæmolysis, one originating in the red cell itself and the other in the cell's environment. These can be quite clearly demonstrated by determining whether the cells in question last a normal length of time when injected into a normal person and, conversely, whether normal cells last a normal length of time in the circulation of a patient in question.

From a practical point of view the first question that confronts us is this: in the clinical and routine laboratory examination of a patient, what findings would lead us to suspect that his erythrocytes are being destroyed prematurely? It should be pointed out here that such findings are based on two simultaneous occurrences: firstly, the more or less sudden release into the blood stream of larger than normal quantities of the products of red blood cell (RBC) disintegration, namely hæmoglobin and red cell debris; and, secondly, the production of anæmia, sometimes with very great rapidity. Some of the important signs which suggest the presence of a hæmolytic process are as follows:

1. Spherocytosis.
2. Spontaneous reticulocytosis (i.e. with no bleeding or hæmolytic treatment).
3. Acholuric jaundice especially associated with dark stools, normal liver and anæmia.
4. Acute anæmia, without hæmorrhage and with chills, back or abdominal pain, red urine.
5. Splenomegaly with any of the above.

The spherocyte is, indeed, the hallmark of the hæmolytic process. It is a small spherical erythrocyte which is thought to result either from a hereditary defect or from injury to the cell membrane. In either case it has, so to speak, the mark of doom upon it. The extent of the spherocytosis usually correlates well with the acuteness of the destructive process. Reticulocytosis simply means that the bone marrow is responding healthily to the stimulus of anoxia (i.e. anæmia). In the absence of hæmorrhage or recent specific therapy in deficiency states it is an indication of blood destruction. Acholuric jaundice is a typical finding when present. The jaundice is rarely intense. In the absence of massive hæmorrhage, acute anæmia points strongly to hæmolysis. The associated chills and fever, back pain, abdominal pain and hæmoglobinuria are due to the products of red cell disruption being released into the blood stream. Splenomegaly in the presence of anæmia is at least suggestive of hæmolytic disease, particularly if the leukocytes and platelets are diminished. The spleen is pre-eminently the erythrocyte "scrap yard", even in health.

Once it has been suspected that a hæmolytic process is present, the next step is to demonstrate that it is. Some of the tests which confirm the presence of premature red cell destruction are listed below.

Absolute

1. The patient's RBC do not survive the usual time in a normal recipient, or normal cells do not survive the normal time in the patient.
2. Hæmoglobinæmia, hæmoglobinuria, hæmosiderinuria.

Relative

1. RBC fragility, osmotic and mechanical. (N.B. increase on incubation.)

*Presented at the Annual Clinical Day of the Hamilton Academy of Medicine, October, 1956.

2. Bilirubinæmia (all "indirect" type).
3. Marrow (normoblastic hyperplasia).

The only direct absolute test is the actual measurement of survival of transfused red cells. This is quite feasible technically using the Ashby technique of serial cross-agglutinations with injected cells, or by tagging the erythrocytes with radio-chromium and observing their rate of disappearance. In either case the rate of loss is plotted against the normal curve. The disadvantages have to do with the time element and the need of a test recipient. Hæmoglobinuria and hæmoglobinæmia are also absolute indications of excessive erythrocyte destruction. Hæmosiderinuria is of the same significance generally and can be tested for by a simple method. There is several days' lag in its appearance in comparison to hæmoglobinuria.

What we might call the *relative* evidences of hæmolytic disease have to do with three types of test: red cell fragility, bilirubin chemistry and bone marrow inspection. Increased osmotic fragility is the classical evidence of a hæmolytic tendency. It is largely due to the presence of spherocytes. The osmotic fragility of blood containing spherocytes is greatly increased after 24-hour incubation. This may be useful in detecting minor degrees of hæmolytic tendency. Increased mechanical fragility is of the same general significance as osmotic fragility and is sometimes tested for in equivocal cases. It must be noted, however, that in some of the hereditary non-spherocytic hæmolytic anæmias due to the abnormal formation of red cells, the fragility may be actually less than normal. Elevated serum bilirubin of the pure indirect type is usually good evidence of hæmolysis. However, the picture is sometimes confused by the presence of so-called "direct" bilirubin produced either by biliary obstruction from liver damage (in acute types) or pigment stones in the common bile duct (in chronic types). The finding of a hyperplastic normal red cell series in the bone marrow is of much the same significance as reticulocytosis, namely, a normal marrow responding to a demand for more erythrocytes.

When the presence of a hæmolytic process has been actually proven, we are next interested in trying to find its causes. This is of the greatest importance, since specific treatment depends upon the identification of etiologic agents. But first let us consider the various kinds of things that produce premature RBC destruction. They may be conveniently divided into those involving defective red cell formation and those involving injury to normally formed red cells. Defective formation can be hereditary or acquired. The four commonest inherited defects result in the production of abnormal-looking red cells. These may become spherical prematurely as in congenital hæmolytic jaundice; they may become crescent-shaped under conditions of anoxia, as in sickle cell anæmia and sickle cell trait; they may be pale, thin, so-called target cells as in Cooley's anæmia and Cooley's trait; or they may be elliptical cells as in elliptocytotic anæmia. These are definite, lifelong entities. One of them, sicklæmia, is apparently entirely due to the remarkable fact that the hæmoglobin molecule is physically and chemically abnormal, so-called hæmoglobin "S". The mechanism of the others is still largely obscure. The relationship of sickle cell anæmia to Negro inheritance and of Cooley's anæmia to so-called "Mediterranean" inheritance is noteworthy.

Intrinsic abnormalities of the erythrocyte may occur occasionally without any evidence of a hereditary factor. The most prominent example is paroxysmal nocturnal hæmoglobinuria. The structural defect here has only very recently been proven by direct observation. Another example is the anæmia due primarily to vitamin B_{12} deficiency, such as pernicious anæmia in relapse, where the erythrocytes are formed abnormally and do not persist for the usual time in the blood stream.

In all of these examples, the hæmolytic tendency is the result of the normal erythrocyte-destroying mechanisms of the body affecting abnormally formed red cells.

In the next group, the basic abnormality is injury to normally formed red cells. This may be brought about by a great many things which can either cause direct damage to the cells or produce it indirectly through the development of some sort of antibody protein which then damages the red cell membrane. The direct effect may be universal, as with chemicals like phenylhydrazine, or idiosyncratic, as with the sulfonamide drugs. The list of these agents is a long one and it is becoming longer every year, as more people are in contact with more and more drugs and chemicals. The following are some proven and some suspected ones:

A. *Drugs.*—Acetanilide; phenacetin; quinine; pamaquin; P.A.S.; sulfonamides; neoarsphenamine; benzedrine; mesantoin? pyribenzamine? benadryl?

B. *Chemicals.*—Amino and nitro compounds of benzol, phenol, toluol; methyl chloride; arsine; phenylhydrazine; some hair dyes; naphthalene; lecithin; lead; etc.

The only positive proof of etiological relationships between a chemical substance and a hæmolytic effect is, of course, its reproducibility. Needless to say, this is sometimes omitted in investigation.

Many living organisms produce substances which are directly injurious to red cells. Injected snake venom, ingested fava bean, infestation with malarial parasite, infection with Bartonella organisms or septicæmic states, to mention a few, may all result in premature red cell destruction.

One of the most interesting hæmolytic states is erythroblastosis fetalis. Here a foreign iso-

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antibody is aroused in the maternal reticulo-endothelial system by an Rh antigen from the developing fetal erythrocytes. This antibody is infused through the placental membrane and injures the baby's erythrocytes, resulting in their wholesale destruction. Rarely, hæmolytic transfusion reactions may be produced in the same manner by unusual iso-antibodies in the infused blood.

It is noteworthy that all of these directly acting hæmolytic agents produce only temporary effects and the blood eventually returns to normal when the agents are dissipated or withdrawn. This, of course, is of considerable practical importance in treatment.

Indirect injury to the red cells occurs for the most part through the medium of antibody proteins which are produced by the patient's own tissues and are therefore called auto-antibodies. There is still a very great deal that is unknown or controversial about these substances but they appear to be mostly globulins which coat the red cell surface membrane, and are in some manner detrimental to it. They cause the cells to become spherical rapidly and to be destroyed prematurely. These antibodies may be specific and contain known red cell antigens of the ABO, Rh, MN, etc., systems but more often they are non-specific. They are usually divided, according to their optimal temperature range, into "warm" and "cold" antibodies, and they are thought to have both a hæmagglutinating and a hæmolyzing activity. Their identification is sometimes very difficult technically.

The manner of production of auto-antibodies is still largely unknown or speculative. However, we do know that infections with certain micro-organisms will produce auto-antibodies capable of resulting in hæmolytic disease. For example, in virus pneumonia cold agglutinins are sometimes produced to a titre high enough to cause hæmolysis. Syphilitic infection has long been known to be related to certain examples of paroxysmal cold hæmoglobinuria. We now know that the blood destruction is brought about by a cold hæmolysin. One of the very disturbing features of auto-antibodies is that they often seem to be self-perpetuating. This may result in long-term illness and necessitate long-term treatment.

It has recently been emphasized that hæmolytic anæmia is often associated with malignancy, especially the various lymphomas including lymphatic leukæmia. It is rather remarkable that this may be the initial manifestation of these diseases, preceding other clinical evidences of them by a year or more.

The relationship between the so-called "collagen diseases" and auto-immune hæmolytic disease is still in the speculative stage. There is good evidence that they are definitely related and both are generally thought of as being "hypersensitivity" diseases.

The spleen takes a direct part in the production of auto-immune hæmolytic disease, since it is the site of some auto-antibody formation. But the role of the enlarged spleen in damaging normal erythrocytes is somewhat uncertain. The congestive changes associated with portal hypertension, for example, may result in very definite hæmolytic effects in some instances. This is sometimes termed "hypersplenism". Finally it must be admitted that there are still factors of etiological importance in the production of some auto-immune hæmolytic disease that are entirely unknown.

But let us return to more strictly practical matters again. We have seen the various pieces of evidence pointing to and confirming the existence of the hæmolytic process. We have seen the various ways in which the hæmolytic process may come about. Now, we can outline the practical ways of identifying these causes at the bedside and in the laboratory.

Six kinds of investigation that could lead to the precise diagnosis are as follows:

1. Family and racial history.
2. History of contact with hæmolytic chemicals.
3. Examination of RBC (morphology–hæmoglobin chemistry–serology including direct Coombs test).
4. Examination of serum (warm and cold antibodies, indirect Coombs test).
5. Identification of other diseases (lymphoma, carcinoma, collagen diseases, infections, portal hypertension).
6. Therapeutic test (steroid, splenectomy).

Family and racial history is largely important in the hereditary erythrocyte formation defects.

Few people would try to remember all of the hæmolytic chemicals. The important thing, of course, is to think of them. Detailed lists are available.

Careful laboratory examination of the morphology, serology and hæmoglobin chemistry of the red cells themselves can often pinpoint the trouble very precisely. Identification of antibody globulins in the serum is a tricky business and must be done with great care and skill to avoid confusing errors. The Coombs tests are, unfortunately, not absolute in their ability to separate hereditary and acquired hæmolytic diseases.

A search must be made for underlying significant diseases. These include lymphoma, carcinoma, infections such as malaria and bacterial septicæmia, collagen diseases, portal hypertension with congestive splenomegaly and so on. Occasionally, despite thorough investigation, uncertainty may still exist as to the etiologic mechanism in a given patient. As in other diseases, a therapeutic test may be justified. The steroids are effective only in certain of the antibody types of disorder. Splenectomy may reveal unsuspected primary splenic disease.

When the presence of hæmolytic disease has been confirmed, and the cause identified as nearly as possible, our attention passes to treatment. There are four general therapeutic categories: (1)the underlying disorder; (2) transfusion; (3) corticosteroids; (4) splenectomy.

1. Treatment of the underlying disorder, if etiologically related, may be lifesaving. It should be noted that this treatment does not necessarily help the hæmolytic process, because of the self-perpetuating nature of some of the auto-antibody mechanisms (as in lymphoma and virus pneumonia). It should be pointed out that identification and elimination of the offending drug or chemical contact is not as easy or obvious as it seems.

2. Transfusion supplies normal red cells to the patient's circulation and relieves the acute symptoms due to anæmia. Symptoms due to the release of products of hæmolysis are not affected. Transfusions are most useful in the acute problems, where they may be lifesaving. The ideal situations are where the primary defect is cellular or where the red cell injury is direct. When the hæmolytic disease is brought about through antibodies, great caution must be exercised to avoid serious and even fatal hæmolytic reactions. If the antibodies are of the specific "iso" type, that is to say, to known human blood-type antigens (e.g. ABO, MN, Rh, etc.), and blood can be found which does not contain them, transfusion is perfectly safe and effective, since the erythrocytes will persist for a normal span in the patient's circulation. This is what is accomplished in the exchange transfusion for erythroblastosis fetalis. If, however, the antibodies are of the "auto" type, particularly if they are non-specific—i.e. will affect all human red cells regardless of their blood type—their injection into the patient's circulation will not produce the desired effects, because they will be rapidly destroyed and additional products of hæmolysis will be released, to the detriment of the patient. There is a further reason for caution in using transfusions when the hæmolytic process is a chronic one. In many instances, a reasonable equilibrium is reached between the blood destructive process and the stimulated bone marrow. Transfusion could upset this balance by reducing the anoxic stimulus to the marrow and the ultimate result would be aggravation of the anæmia. From the practical point of view, then, the grouping and cross-matching laboratory service should not only be given plenty of time to study the compatibilities before issuing blood for transfusion but should also be given plenty of detailed information concerning previous transfusions, any reactions, and all known facts about abnormal antibodies which may be present in the patient's blood. Transfusions should be given as slowly as feasible. Reactions can be somewhat minimized by using saline washed packed red cells and by the use of antihistamines and corticosteroids. The long-term danger of hæmochromatosis from multiple transfusions should be always borne in mind because, in the absence of bleeding, little iron is lost from the body.

3. The third therapeutic approach is the use of corticosteroids and corticotrophic hormones. These drugs are effective only in dealing with red cell injury mediated by antibodies. The mode of action is still rather uncertain. Apparently there is no definite prevention of the formation of antibody. However, interference with the antibody-antigen reaction, to prevent or reduce the lytic or agglutination effect, does appear to occur.

For short-term treatment, cortisone is satisfactory and is the cheapest. Large doses—200 to 300 mg. daily—are in order initially. These may be reduced to 25 to 75 mg. as soon as a satisfactory effect has been achieved. Hydrocortisone seems to have no particular advantages. ACTH for reasons that are not clear may produce favourable responses when cortisone does not. Large doses should be used initially. Slow intravenous administration is by far the most efficient method and this tends to reduce the quite considerable cost. Prednisone and prednisolone are apparently interchangeable. Their chief advantage is their much lessened tendency to produce corticosteroid side effects. They are particularly useful for this reason in patients requiring prolonged administration for months or years. Unfortunately, they are more expensive than cortisone despite the smaller dose. The hazards of long-term steroid use in masking infections and aggravating peptic disease, diabetes and hypertension should be kept in mind throughout the period of administration, no matter how long it may be.

4. The final therapeutic weapon to be considered is splenectomy. It is almost 100% effective in so-called congenital hæmolytic jaundice. This fact emphasizes the very great importance of diagnostic accuracy. This therapeutic result is somewhat unexpected, since the primary abnormality in this condition is a lifelong inherent defect of the erythrocytes. Splenectomy is not particularly helpful in the other hereditary hæmolytic diseases.

In the auto-immune group of acquired hæmolytic anæmias, splenectomy may be effective in 30% to 50% of trials. The favourable results are sometimes temporary, although, interestingly enough, a notable increase in steroid effectiveness has sometimes been observed following splenectomy. The operation in this group is usually preceded by a thorough and frequently prolonged trial of corticosteroids.

The place of splenectomy in so-called hypersplenism is not at all clear-cut since this diagnosis itself is lacking in preciseness. It is nevertheless true that some hæmolytic anæmias, which appear to be caused by disease primarily producing splenic enlargement (e.g. congestive

splenomegaly from portal hypertension, splenic cysts, etc.), may sometimes be remarkably benefited by removal of this organ. In these cases the hæmolytic anæmia is often simply one aspect of a panhæmatocytopenia.

SUMMARY

In summary, four points should be emphasized.

1. Premature destruction of red cells is a cause of anæmia more often than is commonly realized.
2. It is readily detected by standard clinical and laboratory observations.
3. The precise cause of the hæmolytic disease can usually be determined.
4. Treatment of hæmolytic disease may be curative. It is usually quite effective. If used injudiciously it may be useless or even dangerous.

250 Main St. East.

ANNUAL SCIENTIFIC CONVENTIONS

College of General Practice		*Canadian Medical Association*
Winnipeg (April 14-16)	1958	Halifax (June 15-19)
Toronto (April 20-23)	1959	Edinburgh (July 18-25)
Montreal (Feb. 28-March 3)	1960	Banff (June 13-17)
Vancouver (March 20-23)	1961	Montreal (June 18-22)
Halifax (March 6-8)	1962	Winnipeg (June 18-22)

It is the policy of the Executive of the College of General Practice of Canada to plan its annual scientific sessions for the month of March. It is also their policy to meet each year in some part of the country distant from that of the current C.M.A. annual meeting.

DONATIONS TO THE COLLEGE

WHEN THE College of General Practice of Canada was founded in 1954, a Foundation Fund was set up and the Board of Representatives of the College declared that donors of $100 or more would qualify as Foundation Benefactors. A total of $21,455 was contributed to this fund by doctors, which together with the gift of $10,000 from the Canadian Medical Association has permitted the College to function until it is now almost able to meet its expenses from income. The Foundation Fund was closed in June 1956 and was replaced by a Sustaining Fund, for the receipt of further bequests and donations. The second annual report of the College published last June carried a list of Foundation Benefactors. To this list should be added the names of Dr. John Z. Gillies of Toronto, Dr. Max Alexandroff of St. Catharines, Ontario, and Dr. J. D. Ross of Edmonton, Alberta. The College expresses its gratitude to all donors to this Fund and in a recent Bulletin (Vol. 4, No. 1, August 1957) includes a list of donors of less than $100 to the Fund.

MEDICAL MEETINGS

11th INTERNATIONAL CONGRESS OF DERMATOLOGY

The 11th International Congress of Dermatology was held in Stockholm, Sweden, from July 31 to August 6, 1957, and was extremely well attended by representatives of 51 countries throughout the world. Nearly 1000 dermatologists were present, of whom 20 came from Canada. The largest foreign representations were from the United States, Germany, France and Great Britain in that order. Most of the papers were delivered in English but simultaneous translations into French, German and Spanish were provided.

The scientific papers were grouped into main themes, namely biology of skin surfaces, systemic reticulosis, vascular allergy, occupational dermatoses, newer developments in x-ray therapy, and cosmetic dermatology. There were symposia on atopic dermatitis (eczema), antibiotics in dermatology, detergents and barrier creams, bullous dermatoses and histochemistry in skin diseases.

In all these main groups there were times set aside for free communications so that no one was denied the right to submit a paper. Probably the chief impression which the writer obtained was that dermatological problems are much the same throughout the world and problem diseases such as atopic dermatitis are far from being solved. The outstanding scientific contribution of the host city was the presentation of clinical cases, and 100 patients were well shown and documented in the wards of Karolinska Sjukhuset.

The wives and families of the dermatologists were treated to conducted tours about the city and surrounding country, and all those attending were entertained at a monster banquet in the Stockholm City Hall. President Sven Hellerstrom and Secretary General Floden and their confreres and volunteer committees of their ladies are to be complimented on a well-managed international congress. It is planned to hold the next one in the U.S.A. in 1962.

NORMAN M. WRONG,
Toronto

INTERNATIONAL UNION OF THE MEDICAL PRESS

The International Union of the Medical Press held its third congress in London, England, at the home of the British Medical Association, on September 13-15, 1957. At this meeting, 90 editors of medical journals from 29 different countries met under the presidency of Dr. Hugh Clegg, editor of the *British Medical Journal*, to discuss problems common to medical publishing. The meeting was opened by the Congress President, Dr. Clegg, and a message of good wishes from the President of the International Union, Professor M. Loeper of Paris, was read. The Congress opened with papers on "The Press and Medicine" by Dr. A. Plichet, editor of *La Presse Médicale*, of Paris, Dr. S. S. B. Gilder, editor of the *Canadian Medical Association Journal*, Toronto, Dr. O. Josef of Vienna, and Dr. R. Rodewald of Cologne, Germany. It was apparent from these papers and subsequent discussion that the relationship between the daily press and the medical profession has much improved of recent years. Dr. Plichet described the steps taken in Paris to ensure a more cordial liaison between these two groups. Dr. Gilder referred to the code of co-operation with the press, published by the Canadian Medical Association this year, and Dr. Josef and Dr. Rodewald brought news of similar efforts to ensure accurate medical reporting in Austria and Germany.

The second subject discussed at the morning session was "The Editor and the Author", in which scholarly papers were read by Dr. A. M. Cooke, editor of the *Quarterly Journal of Medicine*, and Professor William Doolin, editor of the *Irish Journal of Medical Science*.

The afternoon began with a most useful symposium on illustrations in medical journals; noteworthy among these contributions was that of Mr. Charles Macmillan of Edinburgh, who has spent many years dealing with medical illustrations on behalf of the medical publishers E. & S. Livingstone of Edinburgh. This session was followed by one on standardization of format and bibliographical references, in which papers were read by Professor P. Bonnevie, editor of the *Danish Medical Journal* (*Ugeskrift for Læger*), and Professor J. R. Prakken, editor of the *Dutch Medical Journal* (*Nederlandsch tijdschrift voor geneeskunde*). Reference was made to the very recent publication of the new edition of *World Medical Periodicals*, in which all the known medical journals in the world are listed, together with their abbreviations and details of publication. This reference work is published by the British Medical Association for the World Medical Association, and is the work of Mr. L. T. Morton, information officer of the *British Medical Journal*. This edition contains information in English, French, Spanish and German.

A controversial session on the next morning included material on editorial responsibility for medical advertisements, presented by Dr. J. Garland, editor of the *New England Journal of Medicine*, and Dr. T. F. Fox, editor of the *Lancet*. Dr. Fox in particular was all for adopting a tolerant and liberal attitude towards medical advertising, with the understanding that publishers of a medical journal felt perfectly free to criticize adversely in the editorial sections products advertised in other pages. At a discussion on abstracts or digests, papers were given by Dr. J. Bjorneboe, editor of the *Norwegian Medical Journal*, Dr. D. I. Crowther, editor of *Abstracts of World Medicine*, and Dr. Charles Wilcocks, editor of the *Bulletin of Hygiene*. A discussion on the place of the specialist journal in medical literature was notable for a contribution by Dr. Maurice Campbell, editor of the *British Heart Journal*. The closing session contained contributions from Belgium, Italy and London on multilingual summaries of medical articles. Scientific sessions were followed by a general meeting of the International Union.

The Congress gratefully accepted hospitality from the Royal College of Surgeons, the *Lancet*, the *Practitioner*, the *British Medical Journal*, and the Ciba Foundation. On September 15, delegates visited Cambridge and were entertained at Trinity College. A welcome feature of the Congress was an exhibition of recent British medical books and current British medical journals, conveniently arranged and much appreciated by the delegates.

PUBLIC HEALTH

INFLUENZA IN CANADA

Quebec: The Medical Health Officer of Hull has reported that one school in which 120 children out of 600 were ill with influenza has been closed. At another school 65 pupils out of 500 are sick. The adult population has also been affected. In the County of Temiskaming, 159 absentees in a school population of 745 have been reported; four teachers are also affected.

Ontario: Dr. W. G. Brown, Chief Medical Officer of Health for the province, reports that there has been no major extension of epidemic conditions from the localities previously listed. Two isolations of Asian strain influenza virus have been reported from Sudbury, where the outbreak is said to be declining.

Manitoba: Two Boy Scouts who were ill on arrival in Winnipeg from the Scout Jamboree in England have made satisfactory recoveries. An occurrence of influenza, as yet unconfirmed, is reported from Norway House at the northern end of Lake Winnipeg.

Alberta: The number of service personnel affected by influenza-like disease at Sarcee Military Camp in Calgary, previously reported, has increased from 65 to 300. The occurrence of some 50 cases in the Seventh Day Adventists' College at Lacombe is also reported. Dr. B. Russell, Medical Health Officer of the Minburn-Vermilion Health Unit, has reported

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a localized outbreak of influenza affecting a family at Wainwright. The doctor who collected throat washings from these patients developed a mild respiratory illness two days later.

British Columbia: More than 75 cases of a mild influenza-like disease have been reported at Burns Lake since September 7. The South Central Health Unit, with headquarters at Kamloops, has reported the occurrence of 90 cases of influenza in the Indian Residential School in Kamloops, and some 100 cases in the community. The outbreak commenced about September 1 and is described as mild. An influenza-like disease is reported among 90 of 130 pupils and 11 of 87 staff members at Brannen Lake Boys' School on Vancouver Island. The outbreak, which started on September 1, is described as explosive and was subsiding on September 9.

LETTERS TO THE EDITOR

POSTGRADUATE TRAINING FOR THE G.P.

To the Editor:

There are approximately 12,000 doctors in Canada. Of these, 7000 are G.P.'s. A considerable number of the 5000 specialists are doing general practice—often not doing it well. A similar proportion of G.P.'s are doing specialty work—again often not well. It is doubtful if many specialists want more training in general practice. They are only doing this branch of medicine as a financial necessity. Considerable numbers of G.P.'s do want facilities for postgraduate training enlarged. It is greatly to the credit of the Royal College that they have managed to provide adequate training for their members. In so doing, however, the College has completely cornered all university hospital facilities. This has produced a highly trained body of men, so highly trained and often so specialized that only a large city can offer them adequate scope. Half of the population of Canada is rural and has gained very little by the provision of "adequate numbers" of specialists. General practitioners in these rural areas find themselves doing more and more specialty work as a result of the establishment of small rural hospitals. It is right and just that training should be available to these men. It is not at present, except in the form of extensive diploma courses—the graduates of which do not return to the rural areas. No one specialist trained as he is today can turn his hand from tonsils to ectopic pregnancies, to piles, to acute appendicitis, to compound fractures, to emergency Cæsareans. No modern surgeon can operate an x-ray machine or give electroshock therapy. Alone the G.P. is by temperament, training and location fitted to do and must continue to do this sort of thing in Canada. The argument of course is always raised that less than the complete course will set loose surgical maniacs in Canada. The university authorities must trust the discretion and the judgment of the 7000 as well as the 5000. Indeed the G.P. who lives beside and with his patients is under a greater impetus to judge and act carefully than the super-specialist who manages to insulate himself from his patients outside the operating room. In any case there is only one way to cure surgical mania in the G.P., i.e. give him more training. Unhappily for the man who is a specialist only while in hospital and a G.P. at all other times, we the G.P.'s are here to stay. Moreover it is my personal experience that the G.P. field is ever growing. This is certainly true in rural areas. What must be done? University authorities must give us back our rightful share of university facilities. A start has been made in the form of postgraduate refresher courses. These are well attended and much appreciated but not enough of these are available. It is embarrassing to note for instance that one of Montreal's oldest and yet newest hospitals has no refresher courses for G.P.'s. However, even considerable expansion of facilities in the form of refresher courses is not enough. We must have postgraduate training of at least a year's duration available in university hospitals. The option of doing a year in some specialty or in several specialties is needed. A G.P. who does a year in anæsthesia for instance can make a great contribution to his village or town hospital. A year in surgery can do much to improve a G.P.'s surgery, without at the same time spoiling him for general work in a rural setting.

J. H. S. GEGGIE, M.D.

Wakefield, Que.
August 20, 1957.

ABSTRACTS *from current literature*

MEDICINE

Skeletal Tuberculosis in Children Treated for Primary and Miliary Tuberculosis.

L. MILGRAM: *Am. Rev. Tuberc.*, 75: 897, 1957.

A group of children under 13 years of age with roentgenographic evidence of primary tuberculosis was followed up for two to eight years. During follow-up, skeletal lesions occurred with greatest frequency among the survivors of miliary tuberculosis. The incidence was low among children treated for indications other than miliary disease, including those treated for skeletal tuberculosis, and was lower than in an untreated group. The complication was less frequent under streptomycin and isoniazid treatment than under treatment by the previously used sulfone, Promizole.

These results suggest that the bones are infected early in primary tuberculosis and that chemotherapy acts on already established foci. There is evidence that at the beginning of treatment of miliary tuberculosis, there is widespread involvement of the

bone marrow. Such foci probably account for the frequency of clinical bone tuberculosis in treated generalized tuberculosis. S. J. SHANE

Acute Peptic Ulceration Following Cardiac Surgery.
D. BERKOWITZ, B. M. WAGNER AND J. F. URICCHIO: *Ann. Int. Med.*, 46: 1015, 1957.

Acute peptic ulceration after cardiac surgery was demonstrated in four patients and clinically suspected in three others. This is a most serious complication, for four of the patients died, another surviving only after emergency gastric resection. Prompt diagnosis is essential for a favourable outcome and may be attained only by constant alertness to the possibility. Early surgery, rather than a more conservative program of therapy, may be lifesaving in these patients and should not be withheld merely because the patient has recently undergone cardiac surgery.

Early theories suggested a neurogenic mechanism involving the hypothalamus and the vagal nerves. Hypotension with resulting ischæmia has also been implicated in the pathogenesis. Various stresses may produce an alarm reaction, and during the shock phase acute gastro-intestinal ulcers may form. In two of the patients in this study, prolonged hypotension was present during the operative procedure and immediately afterwards.

This complication arises without any obvious background and without any prodromata—melæna, hæmatemesis or shock being the initial finding. In one patient with perforation, persistent abdominal pain with progressive rigidity was significant, but was clinically misinterpreted. Only one of the patients had had a previous ulcer, and even in this case the source of the fatal hæmorrhage was a new lesion in the stomach. The original site of ulceration was not even grossly apparent.

Until such time as we can predict who will develop these so-called "stress ulcers", the physician must always be on the alert for this possibility. This is especially true for those patients who have responded abnormally to stress in the past.

S. J. SHANE

Multiple Myeloma: Diagnosis and Management in a Series of 57 Cases.
J. J. KENNY AND W. C. MALONEY: *Ann. Int. Med.*, 46: 1079, 1957.

The writers' experience with 57 cases of multiple myeloma over the last nine years confirms the fact that this is not an extremely rare disease. The diagnosis is usually not difficult; pain, anæmia and weight loss in an older person, especially if accompanied by unexplained albuminuria, should arouse suspicion of this diagnosis. Physical findings are usually not helpful except for the rare occurrence of palpable tumour masses, and the diagnosis usually depends on laboratory assistance. While rouleaux formation, rapid sedimentation rate and elevated serum globulin are highly suggestive, the presence of myeloma cells in bone marrow aspirate, Bence Jones protein in the urine, and the characteristic serum and urine electrophoretic patterns are of special diagnostic significance. X-ray evidence of bony abnormalities was present in a high percentage of cases; the presence of osteolytic lesions and pathological fractures is of particular importance.

There is no effective therapy for multiple myeloma. Cortisone or ACTH employed in 16 cases was not helpful. Local intense x-ray therapy to sites of pathological fracture resulted in relief of pain and healing of fracture in two cases. Urethane was used extensively, and approximately 20% of the patients had some benefit from this, but survival time did not appear to be increased by the use of urethane. However, four patients given long-term urethane therapy had prolonged remissions. While it is not certain that this was a direct result of urethane therapy, it is considered that patients with multiple myeloma should be given an adequate trial with this drug. S. J. SHANE

An Evaluation of the Ability of Intermittent Positive Pressure Breathing to Produce Effective Hyperventilation in Severe Pulmonary Emphysema.
J. H. CULLEN, V. C. BRUM AND W. U. REIDT: *Am. Rev. Tuberc.*, 76; 33, 1957.

In normal subjects, intermittent positive pressure breathing produces hyperventilation and a reduction in the carbon dioxide tension principally by increasing the tidal volume. In this study, only 5 of 13 patients with severe emphysema hyperventilated during intermittent positive pressure breathing therapy. Again, when this occurred, it was accomplished principally by increasing the tidal volume.

When there is significant carbon dioxide retention due to emphysema, intermittent positive pressure breathing cannot be relied upon to produce the needed hyperventilation. When oxygen was used to activate the apparatus, hypoventilation occurred in four of six such patients. Although the respiratory rate remained unchanged or increased during intermittent positive pressure breathing therapy in patients with no significant carbon dioxide retention, it fell in those who had an elevated carbon dioxide, especially when oxygen was used to activate the unit. This remained true whether hyperventilation or hypoventilation occurred in response to intermittent positive pressure breathing therapy.

In the emphysematous patients tested, the concurrent use of isopropylarterenol (Isuprel) significantly increased the hyperventilatory response to intermittent positive pressure breathing. In the one patient with carbon dioxide retention who was studied immediately after intermittent positive pressure breathing was completed, the blood gases returned to their pretreatment levels within 15 minutes. Three of the emphysematous patients who responded to intermittent positive pressure breathing with increased ventilation were unable to reduce their carbon dioxide tension by voluntary hyperventilation. S. J. SHANE

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Splenic Rupture in Infectious Mononucleosis.

R. J. HOAGLAND AND H. M. HENSON: *Ann. Int. Med.*, 46: 1184, 1957.

Two cases of infectious mononucleosis with complicating splenic rupture are reported. Both patients were operated on successfully. The authors emphasize that the clinical picture of uncomplicated mononucleosis is not protean and that when unusual clinical manifestations are found, a complication should be suspected. Severe abdominal pain is rare in mononucleosis. When severe or even moderate abdominal pain is complained of, splenic rupture should be considered. Radiation of pain to the left chest and shoulder and an increasing pulse rate strengthen the probability of a ruptured spleen. If a patient with mononucleosis goes into shock, with or without abdominal pain, splenic rupture may be the cause. Prompt operation is of vital importance. Therefore, it is better to explore if the diagnosis is probable, even if the blood count has not yet reflected hæmorrhage, than to wait for convincing hæmatological proof of hæmorrhage.

S. J. SHANE

L.E. Phenomenon in Rheumatoid Arthritis.

I. A. FRIEDMAN *et al.*: *Ann. Int. Med.*, 46: 1113, 1957.

In this study, the L.E. (lupus erythematosus) phenomenon was found in 25 of 91 patients with the classical clinical picture of rheumatoid arthritis. Therapy did not influence the incidence of positive preparations in this study. Rheumatoid nodules, Felty's syndrome and an elevated gamma globulin occurred more frequently in the group with the positive L.E. preparations. None of these patients had pure rheumatoid spondylitis. The patients with the positive preparations were otherwise similar to the patients with negative preparations. Pathognomonic features of systemic lupus erythematosus were not observed in any patient.

It is concluded that the L.E. phenomenon may occur in patients with rheumatoid arthritis as a nonspecific reaction. The diagnosis of systemic lupus erythematosus in such patients, therefore, should be based upon other criteria. S. J. SHANE

SURGERY

Simple Mastectomy for Cancer of the Breast.

B. F. BYRD AND E. STEPHENSON: *Ann. Surg.*, 145: 807, 1957.

Simple mastectomy was the surgical treatment at Vanderbilt Hospital for carcinoma of the breast in 139 cases between 1925 and 1952. Usually the reason was size of the tumour, ulceration and/or extensive lymph node involvement.

The five-year survival rate in this group was 24%, but if there were no metastases evident clinically it was 70%, and with clinical metastases 16%.

No evidence was found that the age of the patient had anything to do with survival, but the average age of patients with metastases when first seen was four years younger than those without. There was no evidence that postoperative radiation improved survival time, or that the duration of symptoms before treatment had any effect either.

Simple mastectomy is reasonable palliative treatment in certain cases of carcinoma of the breast.

BURNS PLEWES

OBSTETRICS AND GYNÆCOLOGY

Localization of the Placental Site by Radioactive Isotopes.

A. WEINBERGE *et al.*: *Obst. & Gynec.*, 9: 692, 1957.

The method of placental localization with radioactive isotopes described is simple, safe and rapid. The procedure can be carried out at the bedside with a minimum of apparatus. The technique can be relied on for a presumptive diagnosis of placenta prævia. Equivocal results sometimes occur when the placenta is located on the posterior uterine wall. The test will be of particular value in antepartum hæmorrhage before the 38th week of gestation. Before definite treatment is undertaken, a positive diagnosis by clinical examination or x-ray placentography is desirable. ROSS MITCHELL

THERAPEUTICS

Treatment of Adenoid Cystic Carcinoma (Cylindroma) of the Respiratory Tract by Surgery and Radiation Therapy.

J. O. VIETA AND H. C. MAIER: *Dis. Chest*, 31: 493, 1957.

Adenoid cystic carcinomas or cylindromas of the tracheobronchial tree are histologically similar to certain neoplasms occurring in the major or minor salivary glands, nasal sinuses, pharynx, palate and other locations. These tumours are apparently derived from mucous glands or ducts occurring in these anatomic areas. In the tracheobronchial tree they are likewise infiltrating tumours with a rather prolonged course in many instances. However, this neoplasm ultimately shows a rather high incidence of metastases both locally to lymph nodes and to distant areas. Their clinical course and much poorer prognosis should distinguish the cylindromas from the carcinoid type of bronchial adenoma which has a comparatively benign clinical course and from other "mixed tumour" types of the tracheobronchial tree with which they are often grouped.

The results of either surgical or radiologic treatment of cylindromas combined with endoscopic procedures cannot be considered good, although the results are better than for the common cancers of the tracheobronchial tree. Apparently when the neoplasm is so situated anatomically that lobectomy or pneumonectomy is possible the therapeutic results are relatively good. However, when the neoplasm extends into the mediastinum or when tracheal resection of any extent is necessary to circumscribe gross disease, a critical re-evaluation at operation should be made, the operative mortality weighed,

and radiation therapy seriously considered. It is apparent that five-year survival without demonstrable disease does not necessarily mean cure by surgery or radiotherapy. This tumour is slow-growing in so many instances that the history of the disease must be appreciated before any claim as to superiority of one form of therapy over another is made. The role of tracheal resection has still to be evaluated. Data on the results of supervoltage radiotherapy for this neoplasm are lacking. Symptomatic relief that follows restoration of an airway may justify palliative resection, but the same may be accomplished often by endoscopic measures and radiotherapy. S. J. SHANE

Chlorpromazine Hepatitis Treated with Cortisone.
M. CUTTS: *Ann. Int. Med.*, 46: 1160, 1957.

The occurrence of jaundice following chlorpromazine therapy has been repeatedly noted, but the exact mechanism of its production remains in doubt. Some authors suggest a drug sensitivity, others an increased viscosity of the bile produced by the medication. Benefit from treatment with cortisone in one case has been reported. This paper embodies a report of another such case, which is presented as an instance of chlorpromazine hepatitis that was promptly benefited by cortisone therapy. If this proves to be the general finding, short-term steroid therapy with its low risk of side-effects would certainly be indicated in most cases. The definite eosinophilia in the reported case was of interest in connection with the possible causative role of sensitivity. S. J. SHANE

Experience with the Course and Chemotherapy of Chronic Pulmonary Histoplasmosis.
W. D. SUTLIFF: *Am. Rev. Tuberc.*, 75: 912, 1957.

The clinical manifestations in 23 cases of chronic pulmonary histoplasmosis confirmed by cultures of *Histoplasma capsulatum* are described. One case with gradual onset and one with advanced pulmonary changes are included.

Special therapy was administered whenever available: Ethyl vanillate was administered in 5 cases; beta-di-ethyl-aminoethyl-fencholate (MRD-112) in 7 cases; Nystatin in 4 cases; and Actidione (2-aminostilbamidine) and cycloserine in one case each. In chronic pulmonary histoplasmosis, definite improvement was noted in only one relatively mild case, following beta-di-ethyl-aminoethyl-fencholate therapy, of a total of 13 cases treated with various agents. Two cases of disseminated histoplasmosis were both arrested after treatment: in the one case with ethyl vanillate, and in the other case with beta-di-ethyl-aminoethyl-fencholate. Toxic symptoms limited the use of all of these agents in varying degrees. A general conclusion was reached that more potent and less toxic antifungal agents were needed for adequate favourable therapeutic effects in chronic pulmonary histoplasmosis. Further trial of these agents in the disseminated form of the disease may be of value. S. J. SHANE

OBITUARIES

DR. CHARLES CAMERON BELL, 82, died on August 16 at his home in Chatham, Ont.

Dr. Bell was born in Chatham and had lived there most of his life. He graduated from the University of Toronto medical school and later qualified M.R.C.S., L.R.C.P. in England. For a few years he practised in New Zealand, and served during World War I as senior director of medical services for Military District I.

He is survived by a son and a daughter.

DR. O. EDMOND CAZA, 64, died at the Hôtel-Dieu Hospital, Valleyfield, Que., on September 22. Dr. Caza was born at St. Anicet, Que., and graduated in medicine from Laval University in 1919. After postgraduate studies in surgery in Winnipeg, Chicago and Rochester, he became chief of the department of surgery at Valleyfield's Hôtel-Dieu Hospital in 1933. He served as mayor of Valleyfield from 1948 to 1953, and had also been president of the Senior Board of Trade, chairman of the school board, and coroner for the district of Beauharnois. He was a former president of the Quebec Division of the Canadian Medical Association and of the medical board of Hôtel-Dieu Hospital.

Dr. Caza is survived by his widow and two sons.

DR. LEOPOLD CHOPIN, 61, died in Montreal early in September. He was born in Montreal and graduated from Loyola College and Laval University in 1922. He was surgeon to St. Luke Hospital, Montreal, for 22 years and at the time of his death was Chief of the Department of Surgery.

He is survived by his widow and two daughters.

DR. REINE AIMEE LACHAINE, 29, died in Ottawa September 4 after a short illness. She was due to start her second year at Johns Hopkins Hospital, Baltimore, where she was studying for a Fellowship in pædiatrics.

Born in Ottawa in 1927, Dr. Lachaîne studied at Bruyère College; after taking her B.A. degree, she went on to Ottawa University, from which she graduated in 1953. She was an intern in pædiatrics at Ottawa General Hospital, and did two years' postgraduate work in that specialty at the Children's Memorial Hospital, Montreal, and one year at Western Reserve University, Cleveland.

Dr. Lachaîne is survived by her parents and a stepbrother and stepsister.

DR. DONALD MALCOLM LINEHAM, 84, died in early September at Vancouver. Dr. Lineham, who was born in Atwood, Ont., studied medicine at McGill University for one year before returning to work with his family in Calgary for three years, after which he returned to McGill to complete his studies. He first practised in Dauphin, Man., and later in Winnipeg. During World War I he served overseas for four years with a Winnipeg battalion. In 1919, he moved to Vancouver, where he re-

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mained in practice until his retirement in 1947. Since that time Dr. Lineham had continued to travel occasionally as ship's surgeon on vessels sailing between Vancouver and Kitimat.

He is survived by two of his daughters.

DR. CHARLES GEORGE GREIG MACLEAN died at Vancouver in August. A native of Fort Augustus, Scotland, he graduated from McGill in 1909. He first practised in British Columbia in 1911 when at Duncan, and was later Assistant Superintendent at Hazelton Hospital. He practised for some time at Smithers and in 1917 went to Woodfibre, leaving there in 1934 to go to Vancouver. During World War II he was in the Army, and then joined the staff of Shaughnessy Hospital, where he served until his retirement in 1955.

Dr. Maclean is survived by a son and two daughters.

DR. JOHN A. McKENNA, 75, who practised as an ear, nose and throat specialist in Toronto for over 50 years, died on September 15. After graduating from the University of Toronto in 1905, he did postgraduate work in Boston. He joined the staff of St. Michael's Hospital, Toronto, as chief surgeon in the otorhinolaryngology department. Some time later he was forced by illness to give up his hospital appointment and went into private practice.

Dr. McKenna is survived by four sisters.

DR. J. A. EWART LINDSAY—AN APPRECIATION

DR. J. A. EWART LINDSAY died of coronary heart disease at Noranda, Que., on September 16, at the age of 53. A graduate of Queen's University in the class of 1928, Ewart Lindsay prepared himself for a busy and useful career, and elected to enter practice in the mining community of Noranda in its early days. He served with distinction during World War II in the R.C.A.F. Medical Branch, 1940-1946. In addition to carrying out the essential but unspectacular duties of a good Medical Officer, he performed an act of bravery which won the award of the George Medal in rescuing the crew of a burning aircraft with a full bomb load in North Africa in 1943. His marriage in 1945 to Nursing Sister Wyn Pitkethly took place in Brussels, an event which has become a romantic legend in the Medical Branch. The tragic death of this good doctor and good citizen recalls the passing in the immediate post-war years of his brother, Dr. Keber Lindsay, who was Secretary of the Saskatchewan Division of The Canadian Medical Association. The Lindsay brothers made substantial contributions to the profession and to the country in peace and war, and their absence makes us the poorer. To Mrs. Ewart Lindsay and to her children, James and Jane, the sympathy of a host of friends is extended.

A.D.K.

MR. JOSEPH A. MURRAY

The passing of Mr. J. A. Murray on September 18, at the age of 76, removes a link in the chain of personalities who have contributed to the development of our Association. Joe Murray was one of the brothers who in 1893 formed a partnership to carry on the Murray Printing Company which had been established by their father.

Since 1919, each issue of the *Canadian Medical Association Journal* has carried in inconspicuous type, "Printed in Canada by the Murray Printing Company", or in recent years, "Murray Printing and Gravure Limited". This long association with our printer began with an act of faith on the part of "Mr. Joe" and his late brother "Mr. Doug". In 1919 The Canadian Medical Association and its Journal were at a low ebb in finance and morale. The Association did not control the publication of its own Journal and to acquire that control it was necessary to purchase it at the cost of $7050 from the former printer and publisher. Such a sum was beyond the meagre resources of The Canadian Medical Association but a committee consisting of Dr. W. W. Chipman, Dr. F. N. G. Starr and Dr. J. W. Scane were able to persuade the foolhardy Murray Printing Company to advance the money and to assume the commercially doubtful privilege of being printers to The Canadian Medical Association. There shortly followed the historic Halifax meeting of 1921 which, confronted with a debt and overdraft exceeding $12,000, took the courageous steps of floating a bond issue among the members and appointing young T. C. Routley as full-time associate secretary.

The turn in the tide was almost immediate because one year later the Executive Committee was able to report that the following debts had been paid:

$5000 owing the Montreal Medical Journal Co.
$3350 to the Murray Printing Company on the Morang account.
$3058 for back printing still owing for 1920.

From these early days the relationship between Murray's and the C.M.A. has been closer than is common between printer and customer. We have observed with satisfaction the growth of our partners in publication and they in turn have been able to serve The Association with understanding as well as efficiency. Mr. J. A. Murray represents a generation of hardheaded and softhearted Canadian businessmen whose vision has done much to build up the country. To his widow, to his sons, Mr. John D. Murray, Executive Vice-President of Murray Printing and Gravure Limited, and Mr. J. Ross Murray, and to his daughters, Mrs. J. C. Anderson and Mrs. G. Norman Cook, we extend the sympathy of The Canadian Medical Association.

A.D.K.

FORTHCOMING MEETINGS

CANADA

CANADIAN SOCIETY FOR THE STUDY OF FERTILITY, Annual Meeting, London, Ontario. (Dr. Morris P. Wearing, Secretary Treasurer, 289 Dufferin Ave., London, Ont.) November 8-9, 1957.

CANADIAN MEDICAL ASSOCIATION, 91st Annual Meeting, Halifax, Nova Scotia. (Dr. A. D. Kelly, General Secretary, The Canadian Medical Association, 150 St. George Street, Toronto 5, Ont.) June 15-19, 1958.

INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS, 2nd Congress, Montreal, P.Q. (Professor Léon Gérin-Lajoie, Suite 313, 1414 Drummond Street, Montreal, P.Q.) June 22-28, 1958.

UNITED STATES

FOURTH PAN AMERICAN PHARMACEUTICAL AND BIOCHEMICAL CONGRESS, Washington, D.C. (Dr. George B. Griffinhagen, Executive Secretary of the Congress, Smithsonian Institution, Washington 24, D.C.) November 3-9, 1957.

CONGRESS OF NEUROLOGICAL SURGEONS, Washington, D.C. (Dr. Philip D. Gordy, Secretary, 1007 Delaware Ave., Wilmington, Del.) November 7-9, 1957.

PAN AMERICAN ASSOCIATION OF OPHTHALMOLOGY, 5th Interim Congress, New York, N.Y. (Dr. William L. Benedict, 100 First Avenue Building, Rochester, Minnesota.) February 1, 1958.

INTERNATIONAL COLLEGE OF SURGEONS, 11th Biennial Congress, Los Angeles, California. (Dr. Karl A. Meyer, Secretary, 1516 Lake Shore Drive, Chicago 10, Illinois.) March 9-14, 1958.

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY, 32nd Congress, New Orleans, Louisiana. (Dr. A. William Friend, Executive Secretary, 227 Wade Park Manor, Cleveland 6, Ohio.) March 24-27, 1958.

INTERNATIONAL SOCIETY OF GASTROENTEROLOGY, 3rd World Congress, Washington, D.C. (Dr. H. M. Pollard, University Hospital, Ann Arbor, Michigan.) May 25-29, 1958.

AMERICAN MEDICAL ASSOCIATION, Annual Meeting, San Francisco, California. (Dr. George Lull, 535 North Dearborn Street, Chicago 10, Ill.) June 23-27, 1958.

OTHER COUNTRIES

CONGRESS OF THE INTERNATIONAL SOCIETY OF SURGERY, Mexico City, Mexico. (Dr. L. Dejardin, 141, rue Belliard, Brussels, Belgium.) October 27-November 2, 1957.

PAN AMERICAN CONGRESS OF ENDOCRINOLOGY, Buenos Aires, Argentina. (Secreteria General, Sociedad Argentina de Endocrinologia y Metabolisma, Santa Fe 1171, Buenos Aires, Argentina.) November 3-9, 1957.

BAHAMAS MEDICAL CONFERENCE, Nassau, Bahamas. (Dr. B. L. Frank, 1290 Pine Ave. West, Montreal, P.Q.) December 1-15, 1957.

INTERNATIONAL ACADEMY OF LEGAL MEDICINE AND SOCIAL MEDICINE, 5th International Congress, Madrid, Spain. (Professor B. Piga, Secretary General of Congress, Professor of Legal Medicine, Madrid University, Madrid, Spain.) April 16-19, 1958.

INTERNATIONAL SOCIETY OF UROLOGY, 11th Congress, Stockholm, Sweden. (Dr. G. Giertz, Secretary General, Karolinska Sjukhuset, Stockholm 60, Sweden.) June 25-July 1, 1958.

COMMONWEALTH HEALTH AND TUBERCULOSIS CONFERENCE, 5th Congress, London, England. (National Association for the Prevention of Tuberculosis, Tavistock House, Tavistock Square, London, W.C.1, England.) July 1-4, 1958.

PROVINCIAL NEWS

NOVA SCOTIA

At the August meeting of the Nova Scotia Medical Society, held in Digby, the Society went on record as expressing dissatisfaction at the lack of opportunity for participation by the Society in decisions reached by the governing bodies concerning health and hospital insurance. It was pointed out that hospitalization intimately affects the whole medical practice of this province. The Society hoped that an opportunity would be given to them to study any proposed moves and to express their opinion before policy decisions are finalized. It was felt that the Medical Society, as a very interested group, had been overlooked in appointments to the hospital planning commission.

Approximately 108 medical men and 60 wives registered at the Digby Pines Hotel as the guests of the Valley Medical Society, for the 104th annual meeting of the Medical Society of the Province of Nova Scotia. The President, Dr. J. R. McCleave, and Mrs. McCleave, entertained members of the executive and their wives at a social gathering on the opening day. This meeting was attended by Dr. A. D. Kelly, Toronto, General Secretary of the C.M.A., and Dr. M. A. R. Young, Chief of Surgery and Medical Superintendent of the Archer Memorial Hospital, Edmonton, and President of the Canadian Medical Association.

The subjects on the agenda for discussion were: medical economics, traffic accidents, rehabilitation, postgraduate education and civil disaster.

At the close of the convention, Dr. A. L. Murphy of Halifax was elected President of the Nova Scotia Division of the C.M.A., and Dr. H. Devereau of Sydney was elected Vice President.

The 105th convention of the Society will be held at Keltic Lodge, Cape Breton, in 1959.

The State University of New York, in Brooklyn, N.Y., has appointed Dr. Gordon R. Hennigar as Professor of Pathology, Associate Director of Laboratories and Pathologist in Chief of the Kings County Hospital. Dr. Hennigar graduated from Dalhousie University in 1945 and on graduation carried out postgraduate work at the Johns Hopkins School of Medicine. For the past seven years he has been Associate Professor of Pathology at the Medical College of Virginia, Richmond.

WALTER K. HOUSE

ONTARIO

Dr. George A. W. Currie has been appointed superintendent of the Hospital for Sick Children, Toronto. He succeeds Joseph H. W. Bower, who recently retired after being associated with the hospital for a number of years during its period of greatest expansion.

To return to his native Canada, Dr. Currie resigned from his post as administrator of hospitals

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and director of facilities, University of Texas, Medical Branch. He was also professor of hospital administration at the University of Texas. Prior to that he was Director of Hospitals for the University of Colorado Medical Center and he was previously administrative assistant at St. Luke's Hospital, New York City.

Born in Picton, Ontario, Dr. Currie received his medical degree from Queen's University. He is also a graduate of the hospital administration course of Columbia University. Dr. Currie has held faculty appointments at several universities and is active in national and international professional and community service groups.

He served overseas in the Royal Canadian Army Medical Corps, retiring with the rank of lieutenant-colonel.

BOOK REVIEWS

A SAMPLE STUDY ON THE PARTICIPANTS OF A CANADIAN PRE-PAYMENT MEDICAL CARE PLAN. Harding leRiche. 168 pp. Illust. Physicians' Services Incorporated, Toronto, 1957.

A study of 2% of subscribers to the comprehensive plan of Physicians' Services Incorporated was made in 1954 and published in 1955, but differed from the present one in not containing great detail about costs in terms of sickness episodes and services. The new study has been carried out on a 2% sample of the 1954 material and contains a fairly detailed analysis of costs, services and sickness episodes classified by main disease groups of the International Classification of Causes of Death, and also in terms of a more detailed list suggested by Trans-Canada Medical Plans.

The material will help administrators to pick out the items which cost a good deal, and will also enable those interested to obtain an over-all picture of the pattern of disease in a large cross-section of the Ontario population. It should be noted that the study does not include costs of hospitalization or drugs, or medical services provided by the state (as for tuberculosis) or the employer (Workmen's Compensation cases).

Dr. leRiche shows that diseases of the respiratory and digestive systems lead in terms of costs and numbers of services. The individual items of high cost in these two groups are tonsillectomy, appendectomy and herniotomy. If the incidence of any one of these operations were to fall sharply, the resultant saving would be great. In the genito-urinary system, surgery of the female genital system accounts for 40% of costs of care. The high cost of operations for hæmorrhoids and varicose veins is also noted. The expenditure on mental illness was found to be less than expected, but much may be hidden under apparently organic diagnoses. Between 13 and 16% of disbursements by P.S.I. are for physiological (including obstetrics) and preventive services. The author remarks: "This is an eminently sound situation and its existence should be clearly recognized."

A comparison made with data from the United Kingdom showed that there is almost certainly more ill health in the U.K. than in Ontario; the difference is particularly marked in respect of diseases of the respiratory system, skin, nervous system and sense organs, locomotor system, infectious disease, and personality and psychotic disorders. In these conditions, the English rates for general practice alone considerably exceed P.S.I. total figures for general practice, specialists and hospital services.

THE PLEA FOR THE SILENT. Anonymous authors. Introduction by Dr. Donald McI. Johnson, M.P., and Norman Dodds, M.P. 176 pp. Christopher Johnson (Publishers), Ltd., London, England; The Ryerson Press, Toronto, 1957. $2.50.

This little spine chiller is the ideal All-Hallowe'en present for both psychiatrist and general practitioner. It consists of eight accounts by mentally sick people of their incarceration and hospital experiences, plus a legal discussion by a well-known lawyer of a particular case. One's first, almost reflex responses are (1) "It didn't really happen that way at all" and then as the accounts tally well with each other and often with one's own experience (2) "It couldn't happen in my practice or in our hospital."

The anonymous authors, all of whom were committed to mental hospitals in Britain, suggest that in their cases the committal procedures were dubious and that once in hospital little or no attempt was made to get them out again or to let them know how they might get out. They do not tell any very horrific tales of open maltreatment. Rather the reverse. But in a way what they do tell is something more frightening. Obvious and open abuses will usually be remedied after a time—but what can one make of the lady who, with little over a week in hospital, was advised to "settle down for life here"? Her failure to take this advice was construed as lack of co-operation and lack of insight—that marvellous piece of psychiatricmanship, where perfect insight means perfect agreement with your psychiatrist's view of you.

Of course no such thing could happen. It was just a delusion, wasn't it? One shouldn't really ask that in cold blood but wait for a gathering of mental hospital superintendents after the evening has nearly gone. It would surprise me if most would not be able to recall hearing advice of that sort given at some time or other during their career. It is the easiest and most tempting thing to adopt the philosophy of "better inside than out". It also leads to no trouble at all. At least it led to very little until this icy little book was published. Things may not be so simple in the future and that is one reason, though not the only one or the best reason, why every practising psychiatrist and G.P. should receive a copy of this work at All-Hallowe'en, if not from his kin, then from a watchful family

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lawyer—or at least it should be on the recommended reading list of medical defence unions.

R. BENSAUDE: Rectoscopie, Sigmoidoscopie (Rectoscopy and Sigmoidoscopy). P. Hillemand, R. Cattan, R. Lambling and A. Bensaude. 270 pp. Illust. 3rd ed. Masson et Cie., Paris, 1956. 6500 Fr. fr.

In 1853 a French surgeon, Désormeaux, first examined the rectum with a metallic tube. Much later, American workers developed the technique; and R. Bensaude, in Paris, made an extensive study of ano-rectal-sigmoid pathology; his last major contribution on the subject was in 1926. This book, written by some of Bensaude's former assistants, brings his work up to date.

The book is remarkable for the colour photographs, which cover practically all aspects of proctological pathology (a total of 40 pages, most showing 4 views at rectoscopy); and there are numerous black-and-white photographs. The text, clear and comprehensive, covers the whole subject, from normal appearances at rectoscopy to those in inflammatory and neoplastic diseases, together with their morphological variations and allied conditions, and including even the rarer ones. To the reviewer this is the most complete and best illustrated account of medical proctology published in many years.

MINIMAL PULMONARY TUBERCULOSIS FOUND BY MASS RADIOGRAPHY (FLUOROGRAPHY): Royal College of Physicians Prophit Tuberculosis Survey. V. H. Springett, Prophit Scholar, 1946-54. 233 pp. Illust. H. K. Lewis & Co. Ltd., London, 1956. £2.2s.

As a result of a Prophit mass radiography survey in the United Kingdom in 1944, a number of small tuberculous abnormalities was revealed in apparently healthy persons. As there was no general agreement as to how these should be managed, it was decided to follow up 1000 cases of patients 15-44 years of age collected between 1946 and 1948 by a similar mass radiography survey. This volume details statistically the results of a five-year follow-up of these 1000 cases.

The radiographic material is classified morphologically, and cases are also classified with respect to social background, clinical features, and laboratory and bacteriological findings. Each chapter concludes with a concise summary of its material, and for the reader interested only in the highlight of the report, reading these will suffice. The follow-up material attempts to relate various initial findings to late results, i.e., to the development or not of active pulmonary tuberculosis. Finally, the "General survey and discussion" chapter covers the entire survey, and in that on "Management of pulmonary tuberculosis" the conclusions derived from the previous work are stated.

In general, no very surprising or unsuspected results are brought to light. Treatment for tuberculosis was given 33.2% of patients within five years of coming under the survey, and 75% of these required treatment within two years. The size of the initial lesion and the presence of tubercle bacilli in the sputum were the most important indications of activity which required active therapy.

This is a well-written report of a well-conducted five-year clinical follow-up of 1000 cases of minimal pulmonary tuberculosis revealed by mass radiography, and will be of interest to all those who are concerned in the treatment of the disease, especially those who work with mass chest radiographic surveys.

DIE GESCHULSTE DER HAUT (Skin Tumours: Clinical and Histological Picture, Recognition and Treatment). Aloys Greither and Helmut Tritsch, Heidelberg. 280 pp. Illust. Georg Thieme Company, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1957. $11.80.

All those skin conditions which have the clinical picture of a tumour are described in the present book. No attempt is made to discuss the theories of origin of tumours, emphasis being particularly laid on a systematic description of the morphology and histology and clinical characteristics of the skin tumours. Therapy is considered only in general terms, without details, for example, of radiation therapy. The extensive bibliography is very up to date and contains a good selection of North American papers. The text is profusely illustrated, mostly with photomicrographs of sections stained by hæmatoxylin and eosin.

ACCIDENTS IN CHILDHOOD. Facts as a Basis for Prevention. Report of an Advisory Group. W.H.O. Technical Report Series No. 118. 40 pp. Illust. World Health Organization, Palais des Nations, Geneva, 1957. $.30.

If we accept an accident as an "unpremeditated event resulting in a recognizable injury", then the problem of accidents in childhood assumes a very important proportion. This highly informative booklet shows that accidents are the leading cause of death in the age groups of one to 19 years, where they are responsible for 30 to 40% of all deaths. Data gathered in several countries show that the highest mortality from accidents is found in the pre-school age, with a second peak in adolescence. The trend in the accident death rate since 1931 in eight countries shows an increase in its percentage of all deaths. Over and above the common forms of accidents reported in the newspapers, such as those from motor vehicles, falls, burning, poisoning, and drowning, the reader is enlightened on the mischievous inventiveness of childhood by the description of such games as "last across the road" in which the more athletic boys dash across the road in front of oncoming traffic and the smaller or weaker ones are caught in the tail of the rush. The attraction of construction yards, vacant buildings, or disused wells is such for children that they account for a substantial proportion of accidents both fatal and otherwise.

This report has been written along epidemiological lines and thus may be more useful to public health authorities than to general practitioners. However, if it will only alert the population at

large to the size and importance of the problem of accidents in childhood, it will have served its purpose.

DIE POSTOPERATIVEN FRUHKOMPLIKATIONEN: IHRE BEHANDLUNG UND VERHUTUNG (Early Postoperative Complications: Their Treatment and Prevention). Kurt Wiemers and Ernst Kern, University of Freiberg. 262 pp. Illust. Georg Thieme Verlag, Stuttgart, 1957. $9.05.

This work is divided into three parts. The first deals with the pathophysiology of the postoperative period. The changes in fluid and electrolyte balance, and respiratory, circulatory and psychic disturbances are discussed thoroughly. The second part covers general and regional complications; the third, treatment and the technical details of it.

This is an unusual and very interesting book and covers an important aspect of surgery. It is well written, up to date in every statement, and a valuable source of information. The illustrations are few but well chosen, and the references to the literature add greatly to its usefulness.

INDIVIDUAL DIFFERENCES IN NIGHT-VISION EFFICIENCY. Medical Research Council Special Report Series No. 294. M. H. Pirenne, F. H. C. Marriott and E. F. O'Doherty. 83 pp. Illust. Her Majesty's Stationery Office, London, 1957. 8s.

In this study of night-vision efficiency, the ability to resolve black Landolt rings of different sizes was measured at different luminance levels. For scotopic vision the absolute thresholds measured by means of a fixation and flash method were found to correlate with the luminance levels used in resolving Landolt rings. In all the experiments the range of uncertainty was great, but this did not obviate the fact that correlations were present.

The results could be explained on the assumption that a filter factor was present in the eye of each subject. This suggests that different subjects are similar as regards scotopic vision, except that one subject may require more light than another to perform a visual task. After training, the score obtained on a perceptual task at standard illumination related to the value of the absolute flash threshold, tending to confirm the filter factor theory.

The quanta of light necessary for a flash threshold and the quanta of light coming from the gaps in Landolt rings during fixation pauses are of the same order of magnitude. The two tasks have a certain similarity.

This monograph deals in a helpful manner with a controversial subject. It can be considered a valuable contribution in the field. The presentation of data showing that there is a relation between perceptual ability and absolute visual threshold, and that this can be explained on a simple light reception variation between individuals, can be considered a significant addition to our knowledge in this area.

This monograph can be recommended to those interested in the field.

SPINAL CORD COMPRESSION. Mechanism of Paralysis and Treatment. I. M. Tarlov, New York Medical College. 147 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $8.25.

This short book summarizes the author's extensive work on experimental spinal cord compression, with the presentation of some clinical material and a list of references that does not pretend to be comprehensive. There is no reference to work done on this controversial subject before the First World War. His carefully executed studies of cord compression by the use of a balloon in the dog's vertebral canal are of some importance, and show that return of function can take place in certain circumstances after complete sensorimotor paralysis. The value of the book undoubtedly lies in the chapters dealing with these experiments. An attempt is made to apply the experimental conclusions to clinical practice. Here the author is faced with the old dilemma—to what extent may the results of animal work be applied to human beings? He does, however, also use clinical facts—his own observations and those of others—to build up his argument. He believes that in all instances (traumatic or non-traumatic) of acute functional transection of the cord, exploration should be undertaken. Many surgeons will take exception to this attitude even after reading the book and will consider the case unproven. When the onset of sensorimotor paralysis is gradual rather than acute, most surgeons would agree that removal of the compressing agent gives reasonable hope of at least some return of function.

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MEMOIRS OF THE SOCIETY FOR ENDOCRINOLOGY. No. 5, The Comparative Endocrinology of Vertebrates. Part II, Hormonal Control of Water and Salt-Electrolyte Metabolism in Vertebrates. Edited by I. Chester Jones and P. Eckstein. 124 pp. Illust. Cambridge University Press, 1956; The Macmillan Company of Canada Limited, Toronto. 25s.

This volume is based on the proceedings of a symposium held in July 1954 at the University of Liverpool. A major portion of the conference was devoted to vertebrate classes below the mammals.

The roles of the neurohypophysis and the adrenal cortex deservedly receive the most attention. The research work presented and discussed is of considerable interest to biologists; it deals with fundamental sites of the action of hormones and for that reason is of value to the clinical endocrinologist. The most stimulating article is that presented by Dr. Conway (University College, Dublin). He discusses his views of the factors controlling ionic distribution across distensible cell membranes, e.g., potassium ions are actively transported into cells by a special carrier. The adrenal mineralocorticoids were shown to act directly on this potassium carrier and only indirectly on the carrier system specific for sodium. Another authoritative contribution, by Dr. Heller of the University of Bristol, deals with the factors activating the neurohypophysis. Several of the contributors discuss the interplay between adrenal cortex and neurohyophysis in the control of water balance.

This book is too complicated for the general reader, but it will be of considerable interest to research workers in human and animal endocrinology.

RYPINS' MEDICAL LICENSURE EXAMINATIONS. Edited by Walter L. Bierring, Iowa State Department of Health. 964 pp. 8th ed. J. B. Lippincott Company, Philadelphia and Montreal, 1957. $10.00.

This book, as its title indicates, presents summaries of the subjects covered by the examinations for licensure in the United States. It is written in a concise and well-organized form with, for the most part, clarity in meaning. Compared with the standard texts a considerable amount of detail has been necessarily omitted from this book. When one considers how searching are many of the questions in the National Board Examinations, it is questionable if many could be answered with the details provided by this book alone. However, in the space of less than 100 pages, each of the 11 subjects covered by the examinations is dealt with in considerable and frequently surprising detail.

The first chapter on medical qualifying examinations is essentially similar to a pamphlet available from the National Board of Medical Examiners and provides examples of the various types of questions (with answers) utilized in the multiple-choice type of examination. The remainder of the book deals with the subjects covered by Parts I and II of the licensing examinations. The material is presented in paragraph form, with bold-type headings for divisions and paragraphs to indicate content and with enumeration or tabulation also in some sections. Following each subject are numerous questions to test one's retention of the material contained in the text. Each section has been written by specialists in the respective field, thus assuring accuracy of content.

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ASIAN INFLUENZA VACCINE IN U.S.A.

The Public Health Service of the United States announced on September 9 that each of the six manufacturers of vaccine against Asian influenza has accepted a proposal to allocate vaccine supplies among the States according to population.

The Public Health Service also announced its endorsement of a recommendation that States and communities establish advisory committees to recommend those who should receive vaccine first, such as key personnel needed to provide medical care and maintain other essential services.

"Any one part of the Nation is as vulnerable as another to a possible influenza epidemic," Dr. W. Palmer Dearing, Acting Surgeon General, pointed out. "A program giving each State and Territory its fair share of the vaccine seems to be the most equitable way of distributing the vaccine geographically throughout the country. As soon as supplies of the vaccine begin to catch up with demand, however, the allocation system may no longer be necessary."

BARIUM GRANULOMA OF THE RECTUM

The accidental introduction of barium particles in the tissues gives rise to a chronic inflammatory reaction and the production of a granulomatous lesion. Gordon and Clyman of New York (*Gastroenterology*, 32: 943, 1957) report three cases of such a lesion in the rectal wall after the administration of a barium enema. The lesion occurs rarely and is clinically silent. It has been suggested that it is probably the result of some minor trauma in the course of this diagnostic procedure and that the granuloma may eventually disappear spontaneously. Its main importance lies in the fact that it may be mistaken for a neoplastic process or for some other chronic inflammatory lesion. On microscopic examination yellow-green crystals are seen surrounded by inflammatory polymorphonuclear leukocytes and lymphocytes. Histiocytes are sometimes present, but multinucleated giant cells are conspicuously absent (at least in the case reported here). However, as the lesion grows older, fibroplastic proliferation, fibrosis and multinucleated foreign body giant cells with intracytoplasmic and free barium sulphate crystals can be observed.

CLINICAL MANIFESTATIONS OF HYPOPOTASSÆMIA

A group of workers from Philadelphia (*Am. J. M. Sc.*, 233: 603, 1957) selected 50 patients with a low blood potassium level for the purpose of evaluating the clinical signs associated with this condition. It soon became evident that patients with the lowest potassium level also had the lowest chloride and calcium levels and that alkalosis was often present. In the group the women were more numerous than the men, presumably because of their inherent lower value for exchangeable potassium. The mortality among the hypopotassæmic patients was strikingly higher than that of the general hospital population. There was only poor correlation between the degree of anorexia and that of hypopotassæmia. Anorexia, nausea and vomiting were present in 84%. However, two patients had a normal appetite with plasma potassium levels of 2.64 and 2.67 mEq./l. In a number of patients who received potassium replacement intravenously, improvement in appetite, enabling oral feeding, followed upon the subsidence of nausea. No correlation was found between the degree of impairment of intestinal motility and the degree of hypopotassæmia. Distension was relieved in some patients with the administration of potassium; others complained of flatulence and painful abdominal cramps while receiving the replacement solution. After administration of potassium the respiratory rate was slower in six patients and faster in five. The evaluation of muscular strength required the co-operation of the patients in squeezing a dynamometer. The authors were not quite satisfied with this method and do not consider the results obtained as valuable. The best correlation was obtained between the

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neuromuscular irritability and the blood potassium level. Absence or significant hypoactivity of the deep tendon reflexes in hypopotassæmic patients before treatment was nearly always associated with a plasma potassium level below 3.0 mEq./l. The authors emphasize, however, that this finding did not manifest its correlation until the study was completed, thus being a very limited diagnostic aid. The most significant changes accompanying infusion of potassium intravenously was the improvement in mental status and the increase in peristaltic activity. In conclusion, the authors point out the importance of laboratory determination and electrocardiography in the diagnosis of this metabolic disorder.

TUMOUR ANTIGENS

An ingenious technique of demonstrating tumour antigens has been evolved by Russian workers and described by Zilber of the Academy of Medical Sciences of the U.S.S.R. (*J. Nat. Cancer Inst.*, 18: 341, 1957). In order to determine whether malignant tumours possess specific antigens not present in corresponding normal tissue, the experimental animal (a guinea pig in the experiments reported) is sensitized to tumour tissue by a subcutaneous injection of the protein fraction of the tissue. About a month later it is injected intravenously with a similar protein fraction, this time of corresponding normal tissue, and desensitized in the usual way by successive injections of small doses of this fraction. The animal is then left in a state in which it will react to any further injection of neoplastic tissue proper and not to any component of normal tissue which could be admixed with it. This test, based on anaphylactic reactions, is highly sensitive and has succeeded in demonstrating such antigens in tumours of animals and human beings. The workers vouch for the absolute sterility and lack of toxicity of their material, so that when anaphylaxis occurred it was interpreted as denoting the presence of tumour antigen. In the case of tumours produced by a virus it is claimed that two antigens were demonstrated, one to the virus and the other to the tumour tissue. Human carcinomas of several different origins were studied; the donor of the normal and that of the tumour tissue were of the same blood group.

UNUSUAL ASPECT OF HYPERTHYROIDISM

Hyperthyroidism may imitate cardiovascular disease to such an extent as to cause confusion in diagnosis. It may also simulate anxiety psychosis, encephalopathy, gastro-intestinal disease with acute abdominal states, rheumatic disease, myasthenia gravis and various oedematous states. Wohl and Shuman have recently reported a series of six cases in *Annals of Internal Medicine* (46: 857, 1957). The presence of a normal or slow pulse does not rule out the possibility of hyperthyroidism, since myocardial damage involving the focus of impulse formation may prevent the occurrence of a tachy-

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cardia. The radiological appearance of a cardiac silhouette resembling closely that encountered in mitral stenosis, with prominence of the pulmonary artery segment, has been reported repeatedly in thyrotoxic heart disease. This finding is all the more confusing as it often follows upon the reporting of an increased mitral first sound and a systolic murmur. The authors claim that 20% of the patients showing cardiovascular manifestations in hyperthyroidism have a normal heart free of any organic lesion. "The remainder have hypertensive or arteriosclerotic cardiac involvement which is incapable of supporting the increased metabolic demands imposed by hyperthyroidism". Exacerbations of hyperthyroid states sometimes give rise to acute abdominal syndromes which have been diagnosed as peptic ulcer, appendicitis, cholelithiasis or colitis. The presence of an abdominal mass has even been reported in some instances. It is only because the surgeon was alert that these patients were spared a useless and even dangerous laparotomy which they would probably have tolerated very poorly. The presenting symptoms and signs subside with control of the hormonal imbalance.

Neurological manifestations may dominate the clinical picture. Disorientation, confusion, convulsive seizures, stupor and coma can be the complaints in this disease. If the neurologic examination is normal, and the only abnormality is a diffuse cerebral impairment revealed by electroencephalography, the cerebral changes are presumed to be functional rather than organic. "While it may be assumed that thyrotoxic encephalopathy is produced by the abnormal metabolic effects of hyperthyroidism upon cerebral tissues, there is no actual information on this point. Clinical observations have been reported on the converse relationships, however, in which cerebral injury has resulted in thyrotoxicosis. A well-known example of this is carbon monoxide poisoning, which may damage the midbrain centres, following which thyrotoxicosis may appear." Although the relationship between the two is not clear, a number of cases of combined hyperthyroidism and myasthenia gravis have been reported. It appears that a therapeutic synergistic effect is produced by prostigmin or any equivalent drug and antithyroid agents. Myxoedema is not the only form of oedema encountered in hyperthyroidism; the authors mention a case in which periorbital and circumoral swelling subsided with antithyroid medication.

AMERICAN HEART ASSOCIATION

The American Heart Association announces that its annual meeting and scientific sessions will be held in Chicago, October 25-29, at the Hotel Sherman. Scientific sessions will this year be dedicated to the tercentenary of the death of William Harvey, and a total of 82 original scientific papers will be presented. The opening day, Friday, October 25, will include a special scientific program for physicians in general medicine, on the prevention and management of cardiovascular emergencies. There will also be a panel on unsettled clinical questions in the

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management of cardiovascular disease. The regular scientific sessions will begin on Saturday morning, October 26, with a brief dedicatory address honouring the memory of William Harvey, and given by Dr. Edgar V. Allen of Rochester, Minnesota, President of the American Heart Association.

There will be two special lectures, the Louis A. Conner Memorial Lecture, to be given by Dr. Charles H. Rammelkamp, Jr., on "Rheumatic Heart Disease, a Challenge"; the other lecture will be the George E. Brown Memorial Lecture to be given by Dr. Nelson W. Barker, of Rochester, Minnesota, on "Current Evaluation of the Thrombosis Problem". The annual dinner of the American Heart Association will be held on Sunday, evening, October 27, at the Hotel Sherman; the guest of honour will be the television star, Ralph Edwards. On the dinner program there will be an address by the incoming president, Dr. Robert W. Wilkins of Boston, professor of medicine, Boston University School of Medicine. Further information from the American Heart Association, Inc., 44 East 23rd Street, New York 10, N.Y.

SNUFF AS A SOURCE OF PATHOGENS

It is rather surprising to find that snuff is used in the United States to the extent of 38 million pounds of tobacco per annum, an average of 0.24 lb. per person in the U.S.A. Dygert (*New England J. Med.*, 257: 311, 1957) indicates that use of snuff should probably be prohibited in patients with chronic bronchitis. He bases this suggestion on a study of a case in which a patient with chronic bronchitis and foul green sputum was found to be coughing up the enteric pathogens *Pseudomonas aeruginosa* and *Proteus vulgaris*. Cultures of the snuff used by the patient revealed the presence of these pathogens; when the use of snuff was discontinued they disappeared from the sputum, which also lost its greenish foul character within a week. It should be noted that antibiotic treatment was given at the same time, but the author points out that these particular pathogens are notoriously resistant to commonly used antibiotics. A further study of 22 samples of snuff from previously unopened containers revealed the presence of the following pathogens: *Staph. aureus, Staph. albus* (coagulase positive), *Ps. aeruginosa, P. vulgaris,* and *B. subtilis.* The author also suggests a further study of organisms contained in chewing tobacco.

POSTGRADUATE COURSES AT NEW YORK UNIVERSITY–BELLEVUE MEDICAL CENTER

The New York University – Bellevue Medical Center Postgraduate Medical School offers during the month of November postgraduate courses in problems in clinical medicine, fundamentals of clinical electrocardiographic interpretation, arthritis and allied rheumatic disorders, electrocardiography, hæmatology, diabetes mellitus, hyperinsulinism and hypoglycæmia, peripheral vascular diseases, culdoscopy, ophthalmoscopy, endaural surgery, review of clinical pædiatrics and pædiatric endocrinology and related metabolism.

CHILDREN IN HOSPITAL

A delightful little booklet has been produced by the staff of the Health Centre for Children, 715 West 12th Avenue, Vancouver 9, B.C., for giving to children threatened with an impending visit to hospital. It contains the story of four-year-old Timothy Dan who has to go to hospital, and it is suggested that parents might read this story to their children before they are taken to hospital. This book contains pictures to colour, a crossword puzzle and other features. It should be helpful to harassed parents.

CIBA MEDICAL RESEARCH FELLOWSHIP, 1958

The Ciba Company Limited, Montreal, invites applications for the Ciba Medical Research Fellowship, 1958. This Fellowship has been established for the training in and promotion of medical research in Canada. The Fellowship is tenable for the year from July 1, 1958, to June 30, 1959. Applications are called for by October 25, 1957, and the appointment will be announced on November 30, 1957. The choice of the Ciba Medical Research Fellow will be made by an independent committee composed of five members.

The Ciba Medical Research Fellowship has a value of $4000; in addition a grant of $500 will be made to the Department where the Fellow will be working to help cover the expenses incurred by the Department in connection with the Fellow's research.

WESTERN DIVISIONAL MEETING, AMERICAN PSYCHIATRIC ASSOCIATION AND WEST COAST PSYCHOANALYTIC SOCIETIES

An attendance of more than 2000 psychiatrists, psychoanalysts and physicians from the Western United States and Canada is expected at the four-day meeting of the Western Division of the American Psychiatric Association in conjunction with the West Coast Psychoanalytic Societies in Los Angeles, California, November 20 through 24.

The meeting, to be held at the Hotel Statler, will be open to members of the American Psychiatric Association, its component District Branches and Affiliate Societies, members and candidates of the Psychoanalytic Societies and Institutes, and their guests.

Papers to be presented will be grouped into the following categories: group psychotherapy, experimental psychiatry, psychosomatic medicine, hospitals, drugs, individual psychotherapy, social psychiatry, child psychiatry, and psychoanalytic papers.

Dr. Ralph W. Gerard, professor of neurophysiology at the University of Michigan School of Medicine, will deliver the Academic Lecture on November 23. Other guest speakers will include Dr. Franz Alexander, Los Angeles, Dr. Sydney Margolin and Dr. René Spitz, Denver, Colorado, and Aldous Huxley.

In addition to presentation and discussion of scientific papers, the meeting will include a series of panel discussions and workshops on "An integrated approach to the objective study of the therapeutic process," "The therapeutic com-

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munity," "Psychological implications of attitudes toward death," and "Tranquillizing drugs and integrating mechanisms: A multidisciplinary approach".

SOME CAUSES OF ITCHING

It was thought at one time that many stimuli to the skin such as a weak constant electrical current or the application of heat below pain threshold would produce itch if of low intensity and pain if of increased intensity. Such a concept does not account for all the modalities encountered in the study of itch. If this sensation is not always chemically mediated, the presence of appropriate nerve receptors must be postulated. According to C. A. Keele *(Proc. Roy. Soc. Med.*, 50: 477, 1957), "the receptors for itch must be situated on the axoplasmic filaments running between, not into, the cells of the epidermis, penetrating as far as the stratum granulosum". Perception of pain may be increased in hyperalgesia when tissues are damaged. Some authors have distinguished between primary hyperalgesia and secondary; the first would involve a lowered threshold for pain, whereas the second would postulate a normal threshold but an exaggerated response to painful stimuli. Some fundamental differences exist between pain and itch. One is that itching is often depressed or abolished when pain occurs. The response to a painful stimulus is a voluntary evasive movement, whereas the response to itching is a scratching movement. Morphine although alleviating pain may render itch worse, whereas barbiturates have an opposite effect at times.

Most investigators have considered histamine as an important etiological factor. In an attempt to explain the difference between urticaria and dermographia, histamine-releasing phenomena which differ in the degree of itch involved, it has been suggested that urticaria releases histamine just beneath or partly in the epidermis but that in dermographia histamine is released in the dermis away from the superficial itch receptors.

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Interesting concepts have come to light from the study of *Mucuna pruriens* or cowhage, the itch powder well known as an old standby of practical jokers, which produces intense itching and even burning when applied to the skin. Cowhage was found to contain very little histamine, but did contain a histamine liberator and also 5-hydroxy-tryptamine. Besides these two substances a proteolytic enzyme known as *mucunain* has been found to play an important part in the itch caused by this powder. Other plant and animal proteinases such as papain, trypsin, chymotrypsin and plasmin can also induce itching. So-called "central itch" has been produced in experimental animals by the application of certain substances to the brain itself. Although no conclusive evidence is available in man, the itch caused by the administration of morphine or that encountered in such diseases as obstructive jaundice, Hodgkin's disease, nephritis and diabetes may well be of the same type. The implication here is that when itching is present and no sign of vasodilatation or whealing can be found, it is very difficult to incriminate the action of histamine.

CONTAGION IN PULMONARY TUBERCULOSIS

An original piece of epidemiological research was carried out in Glasgow. The purpose of this investigation was to answer the following three questions: (1) Is there any danger in occupying a house in immediate succession to a sufferer from pulmonary tuberculosis? (2) Is there a risk in using the same toilet as a person suffering from pulmonary tuberculosis? (3) Is there any risk in having a person with pulmonary tuberculosis as a neighbour? Examination of the social background of 236 patients served as material for the study. The result of the investigation suggested that the source of infection in some patients was from contamination of their houses by previous occupants with pulmonary tuberculosis. Common toilets and tuberculous neighbours were not found to be a significant source of infection as compared to the first one. Among the factors given favouring the survival of tubercle bacilli in the bedrooms of some housing districts of Glasgow is the fact that sunlight does not gain access to most of these rooms very readily, and that windows are commonly kept closed because of the atmospheric conditions. This curtailment of fresh air and ultraviolet light favours the prolongation of infectivity of the dust. It was pointed out, moreover, that toilets are usually very small compartments, all the surfaces of which are easily scrubbed out from time to time with soap and water. *Scottish M.J.*, 2:315, 1957.

COMPLICATIONS OF AORTOGRAPHY

Two reports of renal damage following upon aortography have recently come out in England. A. D. Roy describes a patient on whom aortography was performed and who received first 10 ml. of 30% sodium acetrizoate followed by 25 ml. of 60% solution. The nephro-

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gram showed only the left kidney. The next day, a large hydronephrotic right kidney was uneventfully removed. Five days after the operation the patient became oliguric and his blood urea reached a level of 326 mg. per 100 ml. Later this ascended further to 459 mg. per 100 ml. The patient was given slow intravenous infusions of 50% gluclose in a peripheral vein and fortunately survived. However, his urinary specific gravity does not go now beyond 1.016. The other case reported by a group from St. Mary's Hospital, London, concerns a woman who was admitted to hospital for renal investigation to exclude any secondary cause for her high blood pressure. The day following the aortography she developed a fever and became oliguric. Her urine contained many pigmented granular casts and red cells. Both her kidneys, which had not been palpable before, became easily palpable and tender. Administration of a 40% glucose solution by intragastric drip was prescribed and the patient gradually improved. She had received a preliminary test dose of 5 ml. of 70% diodone, 30 ml. of 70% sodium acetrizoate for the test itself which, unfortunately, was not successful and was therefore repeated with 25 ml. of the same solution. It is interesting to note that whereas both kidneys had been shown to be excreting well and equally during an intravenous pyelogram done some days previously, the second (successful) attempt at nephrogram showed little evidence of excretion on the right side. This was interpreted as indicating immediate damage to the right kidney after the first injection of radio-opaque material. The contrast medium had been inserted into the circulation by percutaneous transfemoral catheterization (Seldinger's technique).

In an annotation on the same topic, it is stated that over 30 cases of serious oliguria have been recorded as an important hazard of aortography. The damage seems to arise mainly from direct injection into the renal arteries or into the aorta immediately between them. The use of large quantities of contrast medium together with any partial obstruction of the terminal aorta increases the risk of injury to the kidneys. The pathological lesion according to the Scandinavian school is that described as "tubular nephritis". Whether this necrosis is due to vascular spasm or is a direct toxic effect is not yet known.—*Lancet*, 2: 16, 18 and 34 (July 6), 1957.

EXPERIMENTAL RESEARCH INTO PROBLEMS OF AGING

The Ciba Foundation, an international centre established for the promotion of international co-operation in medical and chemical research, will grant monetary

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awards in 1958 for original papers on problems of aging. Details of the conditions may be obtained on application to Dr. C. E. W. Wolstenholme, Director, The Ciba Foundation, 41 Portland Place, London, W.1, to whom candidates wishing to compete for the awards should also submit their entries.

Approximately five awards, of an average value of £300 sterling each, are available for the year 1958. The announcement of awards will be made in July 1958. Entries must be received not later than January 1, 1958. They will be judged by an international panel of scientists, who will have power to recommend variation in the size and number of the awards according to the standard of entries. The decisions of the Executive Council will be final. The work submitted may be unpublished, may have been published in 1957, or may be under consideration for publication. The papers may be in the candidate's own language. Papers should not be more than 7000 words in length and a summary in English not exceeding in words 3% of the paper must be attached.

POSTGRADUATE COURSE IN NEUROLOGY

A postgraduate course in adult and pædiatric neurology is offered by the University of Buffalo School of Medicine on October 23 and 24, 1957. It is designed to provide physicians with an understanding of the management of common neurological problems encountered in adult and pædiatric practice. Methods of neurological diagnosis are emphasized through clinical case presentations. Ward rounds enable each registrant to examine a variety of neurological patients and discuss the findings with an instructor. Application for enrolment is to be directed to Milton Terris, M.D., Assistant Dean for Postgraduate Education, University of Buffalo School of Medicine, 3435 Main Street, Buffalo 14, New York. The fee is $30.

GENICULAR ARTHRITIS AND THROMBOPHLEBITIS

Diagnostic confusion may arise from the number of physical signs which are common to acute arthritis of the knee regardless of its etiology and thrombophlebitis of the leg. Bernard Hulbert became interested in this problem after having come across two cases which he reports in the *American Journal of the Medical Sciences* (233:685, 1957). In a survey of 67 cases of genicular arthritis of various causes, Homan's sign was positive in nine; calf tenderness was present in 14, tenderness of the popliteal space in 19, oedema of the foot in eight, and pain on flexion of the knee in all 67. It is interesting to note that Homan's sign was positive in 30% of the cases of rheumatoid arthritis.

RUSSIAN MEDICAL JOURNAL IN ENGLISH TRANSLATION

The Bulletin of Experimental Biology and Medicine, one of the important Russian biological journals, is available in complete English translation from Consultants Bureau, 227 West 17th Street, New York City, at a yearly subscription rate of $20.

This journal covers significant current Soviet research, including papers by leading Soviet biologists

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The Telltale Heart

Carditis is a most serious manifestation of rheumatic involvement. It tells a tale of initial or recurrent streptococcal attack—of organic damage and grave dysfunction. To protect the heart from these consequences is a major objective of BICILLIN prophylaxis.

Recommended by the American Heart Association:[1]

- To prevent rheumatic-fever onset —treatment of streptococcal infections:
  Children—One intramuscular injection of 600,000 to 900,000 units
  Adults—One intramuscular injection of 900,000 to 1,200,000 units

- To prevent rheumatic-fever recurrence—prophylaxis of streptococcal infections:
  Rheumatic-fever patients—One intramuscular injection monthly of 1,200,000 units

1. American Heart Association: Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis, Charles H. Rammelkamp, Chairman: Circulation *15:*154 (Jan.) 1957.

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on physiology, pathology, immunology, biophysics, etc. Each of the 12 issues per year contains more than 20 articles, over 100 pages. Translation began with the 1956 volume, and is presented by special arrangement with the National Institutes of Health. Tables of Contents will be mailed free on request.

Consultants Bureau's English translations of the *Bulletin of Experimental Biology and Medicine* are by scientists, specialists in their fields, equally familiar with Russian and the technical terminology. All material is translated cover-to-cover. Journals are staple-bound, and include all diagrams, photographs and tabular matter integral with the text.

LONDON THYROID CLUB AND AMERICAN GOITER ASSOCIATION

The London Thyroid Club and the American Goiter Association have announced that the Fourth International Conference on Goiter will be held in London, England, in 1960. Scientific sessions will be held in the Royal College of Surgeons on July 6, 7 and 8, 1960.

Those who desire to submit abstracts of papers for consideration for inclusion in the program should write to Selwyn Taylor, F.R.C.S., 3 Roedean Crescent, Roehampton, London, S.W. 15, England; or to John C. McClintock, M.D., 149½ Washington Avenue, Albany 10, New York, U.S.A.

Travel and hotel accommodations may be secured from Thomas Cook and Sons, Ltd.

A very few honoraria will be available for travel assistance. For further particulars contact either of the above.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The Part I Examinations of the American Board of Obstetrics and Gynecology are to be held in various parts of the United States and Canada on Thursday, January 2, 1958, at 2:00 p.m.

Candidates notified of their eligibility to participate in Part I must submit their case abstracts within 30 days of notification of eligibility. No candidate may take the written examination unless the case abstracts have been received in the office of the Secretary.

Current Bulletins outlining present requirements may be obtained by writing to the Secretary's office: Robert L. Faulkner, M.D., American Board of Obstetrics and Gynecology, 2105 Adelbert Road, Cleveland 6, Ohio.

RESEARCH IN NEUROMUSCULAR DISEASES

The Sister Elizabeth Kenny Foundation announces a continuance of its postdoctoral scholarships to promote work in the field of neuromuscular diseases. These scholarships are designed for scientists at or near the end of their fellowship training in either basic or clinical fields concerned with the broad problem of neuromuscular diseases.

Kenny Foundation Scholars will be appointed annually. Each grant

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provides a stipend of from $5000 to $7000 a year for a five-year period, depending upon the Scholar's qualifications. Candidates from medical schools in the United States and Canada are eligible.

Inquiries concerning details should be sent without delay to: Dr. E. J. Huenekens, Medical Director, Sister Elizabeth Kenny Foundation, 2400 Foshay Tower, Minneapolis 2, Minnesota.

NATIONAL CANCER INSTITUTE OF CANADA RESEARCH GRANTS

The National Cancer Institute of Canada offers financial support for new as well as established worthy research projects which may be related to a furthering of general knowledge concerning cancer. These grants are made to individuals with research experience for the purchase and maintenance of animals and equipment for expendable supplies and for the payment of technical and research assistants.

Limited expenses incurred by travelling for scientific purposes are considered separately and requests for such grants should be submitted to the Executive Director. In general, such travelling grants will be made for the purpose of presenting a paper at a scientific meeting or of learning a new technique in cancer research.

Research grants commence on April 1 and terminate on March 31. Application forms may be obtained from the Institute and five copies should be submitted by December 15. They should always be completed in a detailed manner so that the referees may make a comprehensive appraisal of the project or its progress and the intended use of the research grant.

Late applications will be considered in special circumstances, but a decision on such an application may not be possible for several months after it is received.

Address all communications to: Executive Director, National Cancer Institute of Canada, 800 Bay Street, Toronto 5, Ontario.

THE FORENSIC SOCIETY OF CANADA

The Forensic Society of Canada will hold its Fifth Annual Meeting at the Sheraton-Mount Royal Hotel in Montreal on November 7, 8 and 9, 1957. Among the subjects discussed will be bone identification, pathology, radiochemistry, metabolism of toxicological organic compounds, alcohol analysis and the structure of various drugs and naturally occurring compounds, in the urine.

The Society, formed in Ottawa in 1953, is made up of a group of about 50 scientists, police officers and lawyers who are interested in promoting better understanding between the legal societies, medical societies and other scientific organizations engaged in forensic work. They are particularly interested in establishing a liaison with the medical profession in general, and extend an invitation to all physicians interested in this aspect of practice to attend their annual meeting. Further information can be obtained from Mr. H. N. MacFarland, Secretary-Treasurer, The Forensic Society of Canada, 200 Kent Street, Ottawa.